IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) **DEMAND FOR JURY TRIAL**
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff/Counter Defendants.	

EXHIBIT 15B

SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 2 TO EXCLUDE EVIDENCE OR ARGUMENT THAT NS'S COMMERCIAL PRODUCT (VILTEPSO) PERFORMS BETTER THAN SAREPTA'S COMMERCIAL PRODUCT (VYONDYS 53)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 2 TO EXCLUDE EVIDENCE OR ARGUMENT THAT NS'S COMMERCIAL PRODUCT (VILTEPSO) PERFORMS BETTER THAN SAREPTA'S COMMERCIAL PRODUCT (VYONDYS 53)

[redacted]

NS should not be allowed to argue or suggest that its product, VILTEPSO, performs better than Sarepta's VYONDYS 53. There has never been a head-to-head clinical trial of the two products. There have only been individual studies of the products that were not designed to be, and cannot be, compared. As a result, the FDA does not allow either party to promote its product as superior to the other. The same should be true in this Court, especially given the disparate methodologies, patient populations, and other major differences in the studies. Any comparison of efficacy or safety is scientifically unsound and irrelevant under Fed. R. Evid. 401.[1] Moreover, any probative value is far outweighed by the danger of unfair prejudice, confusing the issues, misleading the jury, and wasting time (Fed. R. Evid. 403), particularly when NS's asserted patents do not even cover NS's VILTEPSO. Ex. A at 18. NS can certainly argue that the products are both FDA-approved, safe and effective, and compete for the same patients. But it should not be permitted to say or suggest that VILTEPSO is better than VYONDYS 53, or otherwise criticize the safety or efficacy of VYONDYS 53. This is not a case about which product is better, and litigating that issue would require a "mini-trial" within an already-complex and compressed trial, with a high likelihood of jury confusion.

NS may argue that it does not intend to go beyond what the FDA allows, *i.e.*, it will not make express head-to-head comparisons. Yet, based on its expert reports, NS intends, at a minimum, to strongly suggest that its product is better. For example, in support of its lost profits claim, NS argues that "VYONDYS 53 was likely ***more difficult to promote*** than VILTEPSO due

[1] *See Hill v. GEO Group, Inc.,* No. 1:18-CV-01363, 2021 WL 6053783, at *5–6 (W.D. La. Dec. 21, 2021) (excluding testimony based on tests "not approved by the FDA for accuracy or clinical use"); *Hosbrook v. Ethicon, Inc.*, No. 3:20-CV-88, 2021 WL 4452289, at *3 (S.D. Ohio Sept. 29, 2021) (FDA process for clearing medical devices "concerns 'equivalence, not safety'" and "is not relevant [to product liability] since it does not establish that the Prolift is safe and effective").

[redacted]

to its low dystrophin [*i.e.*, protein missing in Duchenne muscular dystrophy] production and highly publicized comments from the FDA doubting the clinical benefit of the treatment relative to the risk." Ex. B at 15 (emphasis added).[2] It is undisputed that FDA does not allow NS to promote VILTEPSO as superior to VYONDYS 53, because there are no head-to-head studies.[3] *See* Ex. F at 77:3–11 (NS is not "allowed to create marketing materials that directly compare VILTEPSO and VYONDYS [53]" because "[t]here are no head-to-head studies"); Ex. G at -395 ("We cannot make any direct comparisons of [VILTEPSO] to other investigational therapies for DMD, as there have been no head-to-head studies.").

NS's comparison of VILTEPSO and VYONDYS 53 is not based on reliable principles and methods (*see* Fed. R. Evid. 702), and is therefore irrelevant. The studies NS relies on (*e.g.*, Exs. H–L) were not designed to compare the drugs, and they differed in ways that prevent meaningful comparison. The Western blot assay used to measure dystrophin levels is influenced by differences in sample collection and processing, controls, and quantitation methodology; such data cannot be compared across studies. Ex. M at 98:2–5 ("FDA agrees that a comparison should not be made of dystrophin values following treatment with VYONDYS 53 and VILTEPSO."). Limitations of sample size, and differences in patient demographics and baseline disease, likewise prevent comparison of motor function outcomes.[4] *See* Ex. F at 81:23–82:5 ("NS Pharma cannot make that comparison."); *see also* Ex. M at 105:14–19 ("nobody really knows" "how elevated a

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[2] *See also id*. at 5 (same reasons support opinion that "NS Pharma could have sold more units of VILTEPSO and at a faster rate than VYONDYS 53"); Ex. C at ¶¶ 64–67 ("these differences would favor starting VILTEPSO over VYONDYS 53"); Ex. D at ¶¶ 6–26 ("the [redacted] change in baseline dystrophin levels following VILTEPSO treatment favors its use over VYONDYS 53"; "[while] there was no significant functional benefit of VYONDYS 53 treatment, there were functional benefits reported for VILTEPSO").

[3] For all its bluster, [redacted]. *Compare* Ex. E Tab 8 at cells BA1–BP1 with *id*. Tab 10 at cells AN1–BC1.

[4] It is undisputed that the products have similar safety profiles. *See* Ex. M at 75:12–14.

[redacted]

DMD patient's dystrophin level has to be to make a functional difference"). On the basis of lack of relevance alone, the Court should grant this motion. *See Hosbrook*, 2021 WL 4452289, at *3 (FDA process for clearing medical devices "concerns 'equivalence, not safety'" and "is not relevant [to product liability] since it does not establish that the Prolift is safe and effective").

Any arguable relevance is far outweighed by the danger of unfair prejudice, confusing the issues, misleading the jury and wasting time. VILTEPSO is not a commercial embodiment of NS's asserted patents, and it would be manifestly unfair for NS to confuse the jury by comparing the parties' commercial products. Sarepta would also be unfairly prejudiced by the large amount of time required to address NS's argument in an already-complicated and abbreviated trial schedule. Each side has asserted patents, and there are a host of issues for the jury to decide (including for example written description, enablement, obviousness, willfulness and possibly damages). Another time-consuming "mini-trial" to decide whether NS's product is better than Sarepta's would be both unfair and a waste of time. *See, e.g., Zimmer v. Stryker*, No. 16-679, 2019 WL 9244877, at *1 (D. Del. Mar. 15, 2019) (probative value "is substantially outweighed by the danger of unfair prejudice, confusing the issues, and having a mini-trial on [the evidence]").

NS can explain the benefits of its product, point out that the FDA has deemed it safe and effective, and argue that the companies' products compete for the same patient population, to support its lost profits claim. But any argument or evidence that its product is superior to Sarepta's, or any criticism of VYONDYS 53, is unnecessary, unsupported by the facts and unfairly prejudicial. Permitting a jury trial on those satellite and irrelevant issues would create a sideshow in an already-complicated trial. The Court should grant this motion, and preclude NS from presenting evidence or argument at trial suggesting that VILTEPSO is better than VYONDYS 53, or otherwise criticizing the safety or efficacy of VYONDYS 53.

[redacted]

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CERTIFICATION PURSUANT TO LOCAL RULE 7.1.1

Defendant and Counter-Plaintiffs Sarepta Therapeutics Inc. and the University of Western Australia certify that a reasonable effort has been made to reach agreement with Plaintiff and Counter-Defendants Nippon Shinyaku Co., Ltd. and NS Pharma, Inc. regarding Counter-Plaintiffs' Motion *in Limine* No. 2. The Parties were unable to reach agreement, and Counter-Defendants refused to agree to Counter-Plaintiffs' requested relief.

/s/ Megan E. Dellinger

Megan E. Dellinger (#5739)

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH)
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

[PROPOSED] ORDER GRANTING SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 2 TO EXCLUDE EVIDENCE OR ARGUMENT THAT NS'S COMMERICAL PRODUCT (VILTEPSO) PERFORMS BETTER THAN SAREPTA'S COMMERICAL PRODUCT (VYONDYS 53)

At Wilmington this _____ day of _____, 2024, having considered Defendant and Counter-Plaintiffs Sarepta Therapeutics, Inc. and the University of Western Australia's Motion *in Limine* No. 2 to Exclude Evidence or Argument that NS's Commercial Product (VILTEPSO) Performs Better than Sarepta's Commercial Product (VYONDYS 53), and all papers and arguments submitted therewith, IT IS ORDERED that the motion is GRANTED. Plaintiff and Counter-Defendants Nippon Shinyaku Co., Ltd. and NS Pharma, Inc. are precluded from presenting evidence or argument suggesting that their commercial product, VILTEPSO,

performs better than Sarepta's commercial product, VYONDYS 53, or otherwise criticizing the safety or efficacy of VYNODYS 53.

_____
United States District Judge

CERTIFICATE OF SERVICE

I hereby certify that on April 19, 2024, copies of the foregoing were caused to be served upon the following in the manner indicated:

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EXHIBIT A

UNITED STATES DISTRICT COURT

DISTRICT OF DELAWARE

Case No. 1:21-cv-01015-GBW

NIPPON SHINYAKU CO., LTD.,

Plaintiff,

v.

SAREPTA THERAPEUTICS, INC.,

Defendant.

SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA,

Defendant and Counter-Plaintiffs,

v.

NIPPON SHINYAKU CO., LTD., and NS PHARMA, INC.,

Plaintiff and Counter-Defendants.

EXPERT REPORT AND DISCLOSURE OF MARK J. HOSFIELD

Submitted September 8, 2023

[redacted]

The authors concluded that "[b]ased on the results of this 4-year LTE, viltolarsen can be an important treatment strategy for DMD patients amenable to exon 53 skipping."[93]

The wholesale acquisition cost ("WAC") of VILTEPSO has been $1,410 per vial since it launched.[94] As described later in this report, VILTEPSO is manufactured outside the U.S.[95] Since its launch in August 2020 through 2022, the total number of patients on VILTEPSO increased to 95.[96]

I understand that VILTEPSO does not practice the NS patents-in-suit. More specifically, I understand that NS Japan lists two patents in the Orange Book Patent Data for VILTEPSO.[97] These two patents are U.S. Patent No. 9,079,934 entitled "Antisense Nucleic Acids," issued on July 14, 2015, and U.S. Patent No. 10,870,676, also entitled "Antisense Nucleic Acids," issued on December 22, 2020.[98] Both of these patents are related to the NS patents-in-suit.[99]

ii. VYONDYS 53

The active ingredient in VYONDYS 53 is golodirsen.[100] Sarepta developed Golodirsen in collaboration with University College London, and Royal Holloway, University of London as part of the SKIP-NMD grant.[101] According to Frederick Schnell, Ph.D., Director of Business Development at Sarepta, the SKIP-NMD grant "was a grant that a consortium of academic incorporations procured to develop an exon 53 skipping PMO."[102]

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[93] https://content.iospress.com/articles/journal-of-neuromuscular-diseases/jnd221656.

[94] Deposition of Gardner Gendron, dated July 11, 2023, p. 49.

[95] Deposition of Kazuchika Takagaki, Ph.D., dated June 13, 2023, pp. 75-76.

[96] NS00140986.xlsx, 'Forecast Model – Stretch' tab.

[97] https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=212154&Appl_type=N.

[98] U.S. Patent No. 9,079,934 entitled "Antisense Nucleic Acids," issued July 14, 2015; U.S. Patent No. 10,870,676, entitled "Antisense Nucleic Acids," issued December 22, 2020.

[99] U.S. Patent No. 9,079,934 entitled "Antisense Nucleic Acids," issued July 14, 2015; U.S. Patent No. 10,870,676, entitled "Antisense Nucleic Acids," issued December 22, 2020; see, for example, U.S. Patent No. 10,385,092 entitled "Antisense Nucleic Acids," issued August 20, 2019.

[100] Deposition of Ethan Jacoby, dated June 22, 2023, p. 15; O'Malley Exhibit 15: VYONDYS 53 Label, dated December 2019 (SRPT-VYDS-0211289-SRPT-VYDS-0211303 at SRPT-VYDS-0211296).

[101] Deposition of Frederick Schnell, Ph.D., dated July 26, 2023, pp. 184-186; Schnell Exhibit 18: Research Report: Selection of PMO Sequence for Exon 53 SKIP-NMD Grant# 305370, dated September 4, 2014 (SRPT-VYDS-0201524-SRPT-VYDS-0201588); Deposition of Emily Naughton, dated July 12, 2023, p. 26.

[102] Deposition of Frederick Schnell, Ph.D., dated July 26, 2023, pp. 128-129.

Reasonable Royalty Damages

	Dec. 12, 2019 - Dec. 31, 2019	2020	2021	2022	Jan. 1, 2023 - Mar. 31, 2023	Total
Reasonable Royalty						
U.S.Paid Units						
U.S. Free Units						
Foreign Units						
Total Reasonable Royalty Units						
Royalty Rate						
Total Reasonable Royalty Damages						

In addition, I have also calculated the legal fees incurred by NS Japan that I understand are related to Sarepta's alleged breach of the MCA, consisting of "IP Litigation" fees of $ and total "PTAB" fees of $.[594]

****

My report, with supporting exhibits, is contained herein, and presents a summary of my opinions and the bases and reasons therefor as of this date. To the extent any additional information is produced by the parties or their experts, I will be prepared to incorporate any such additional information into my report, or otherwise to amend or supplement my report as appropriate.

This report is to be used only for the purpose of this litigation and may not be published or used for any other purpose without prior written consent.

By:

Mark J. Hosfield
September 8, 2023

[594] Exhibit 7, Schedules 1 and 2.

EXHIBIT B

UNITED STATES DISTRICT COURT

DISTRICT OF DELAWARE

Case No. 1:21-cv-01015-GBW

NIPPON SHINYAKU CO., LTD.,

Plaintiff,

v.

SAREPTA THERAPEUTICS, INC.,

Defendant.

SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA,

Defendant and Counter-Plaintiffs,

v.

NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC.,

Plaintiff and Counter-Defendants.

REPLY EXPERT REPORT AND DISCLOSURE OF MARK J. HOSFIELD

Submitted October 27, 2023

[redacted]

As an initial matter, I understand from Mr. Gendron that had VYONDYS 53 never entered the market, NS Pharma would have anticipated receiving accelerated approval from the FDA it is reasonable to assume that the FDA would have accelerated the approval of VILTEPSO, leading to an earlier launch. Indeed, Mr. Gendron further explained to me that NS Pharma had anticipated the possibility as early as four weeks after Sarepta received its complete response letter from the FDA denying its new drug application ("NDA") for VYONDYS 53 on August 19, 2019.[15] Such an event would undercut the premise of Mr. Jarosz's ramp-up approach, further proving the speculative nature of the approach.

However, even assuming the FDA did not accelerate the launch date of VILTEPSO, there is still reason to believe that VILTEPSO may not have experienced a ramp-up period similar to that of VYONDYS 53. For example, I understand from my discussion with Mr. Gendron that because it was known that 1) the FDA did not initially approve Sarepta's NDA for VYONDYS 53 because it found that the "very small" clinical benefit of VYONDYS 53 did "not outweigh its risks,"[16] and 2) although direct comparisons cannot be made across studies, dystrophin levels induced by VILTEPSO [redacted],[17] he believes NS Pharma could have sold more units of VILTEPSO and at a faster rate than VYONDYS 53.

Mr. Jarosz also criticizes my assumption that NS Pharma would have been capable of making such additional sales. For example, while he acknowledges my conversations with NS Japan personnel for support of my understanding that NS Japan and NS Pharma would have had the capacity to achieve such sales, he states that "as a matter of economics, it is likely such a dramatic increase in sales would have had some impact on NS Japan or NS Pharma's supply chain. Mr. Hosfield has provided no documentary proof of either company's ability to expand its production to such but-for levels."[18] I have discussed in my Opening Report Mr. Gendron's testimony that NS Pharma's "drug supply is ample"[19] to meet the U.S. demand, as well as my understanding from Mr. Fujii and Dr. Takagaki that NS Japan would have had the flexibility to expand

[15] U.S. Food & Drug Administration Complete Response Letter to Sarepta Therapeutics, Inc., dated August 19, 2019 (NS00096434-NS00096446 at NS00096442).

[16] U.S. Food & Drug Administration Complete Response Letter to Sarepta Therapeutics, Inc., dated August 19, 2019 (NS00096434-NS00096446 at NS00096442).

[17] Safety, Tolerability, and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping, A Phase 2 Randomized Clinical Trial (NS00035339-NS00035348 at

[18] Rebuttal Expert Report of John C. Jarosz, dated October 11, 2023, p. 53.

[19] Rebuttal Expert Report of John C. Jarosz, dated October 11, 2023, p. 53.

Agreement, as detailed in the attached Exhibit 3A, Schedule 3 to my Opening Report, I have used NS Pharma's [redacted][73] Thus, because Mr. Jarosz's suggested additional $[redacted] is calculated using NS Pharma's expenses as of August 19, 2020, it does not account for the additional $[redacted] that NS Pharma spent prior to the launch of VILTEPSO.[74] I understand from my discussion with Mr. Gendron [redacted]. These expenses included [redacted], among other things.[75] In considering the above facts, Mr. Jarosz's calculation of an additional $[redacted] in marketplace creation expenses would be duplicative and result in lost profit damages that are understated.

To the extent Mr. Jarosz believes that, in order to achieve the additional lost sales, NS Pharma would have to spend even more upfront marketing expenses on top of the $[redacted] it had already spent, there are factors which suggest otherwise. For example, because there was a long felt need for DMD treatments for patients with mutations amenable to exon 53 skipping,[76] Mr. Gendron explained that VILTEPSO would have benefitted from the market awareness of ASO products created by Sarepta's EXONDYS 51 product.[77] He further explained to me that NS Pharma likely would not have had to spend as much upfront for VILTEPSO as Sarepta did for VYONDYS 53 because VYONDYS 53 was likely more difficult to promote than VILTEPSO due to its low dystrophin production and highly publicized comments from the FDA doubting the clinical benefit of the treatment relative to the risk.[78]

[73] Expert Report and Disclosure of Mark J. Hosfield, dated September 8, 2023, Exhibit 3A, Schedule 3 and Appendix A.

[74] Calculated as [redacted]

[75] Discussion with Mr. Gendron.

[76] Rebuttal Expert Report of Stanley Nelson, M.D., dated October 11, 2023, p. 8; Rebuttal Technical Expert Report of Jonathan Strober, M.D., dated October 11, 2023, ¶ 12.

[77] Discussion with Mr. Gendron.

[78] Discussion with Mr. Gendron; U.S. Food & Drug Administration Complete Response Letter to Sarepta Therapeutics, Inc., dated August 19, 2019 (NS00096434-NS00096446 at NS00096442).

	Reasonable Royalty Damages
Reasonable Royalty	[redacted]
U.S. Paid Units	
U.S. Free Units	
Foreign Units	
Total Reasonable Royalty Units	
Royalty Rate	
Total Reasonable Royalty Damage	

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My Reply Report, with supporting exhibits, is contained herein, and along with my Opening Report and Rebuttal Report, presents a summary of my opinions and the bases and reasons therefor as of this date. To the extent any additional information is produced by the parties or their experts, I will be prepared to incorporate any such additional information into my reports, or otherwise to amend or supplement my reports as appropriate.

This report is to be used only for the purpose of this litigation and may not be published or used for any other purpose without prior written consent.

By:

Mark J. Hosfield
October 27, 2023

EXHIBIT C

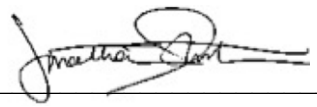
[redacted]

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (GBW)
SAREPTA THERAPEUTICS, INC., Defendant and Counter-Plaintiff, and UNIVERSITY OF WESTERN AUSTRALIA, Counter-Plaintiff v. NIPPON SHINYAKU CO., LTD., Plaintiff and Counter-Defendant and NS PHARMA, INC., Counter-Defendant.	

TECHNICAL EXPERT REPORT OF JONATHAN STROBER, M.D.

SEPTEMBER 8, 2023



JONATHAN STROBER, M.D.

64. Based on the published data for each of VILTEPSO and VYONDYS 53, at least some patients have experienced a benefit of taking these exon skipping products, as reflected by the primary endpoint measured – increase in dystrophin production. For example, in the clinical trials for each of VILTEPSO and VYONDYS 53, efficacy was measured by change from baseline in dystrophin protein level at a certain time period after treatment (which differs between products):

VILTEPSO[51]	VYONDYS 53[52]
"Efficacy was assessed based on change from baseline in dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 25. Muscle biopsies (left or right biceps brachii) were collected from patients at baseline and following 24 weeks of VILTEPSO treatment, and analyzed for dystrophin protein level by Western blot normalized to myosin heavy chain (primary endpoint) and mass spectrometry (secondary endpoint). In patients who received VILTEPSO 80 mg/kg once weekly, mean dystrophin levels increased from 0.6% (SD 0.8) of normal at baseline to 5.9% (SD 4.5) of normal by Week 25, with a mean change in dystrophin of 5.3% (SD 4.5) of normal levels (p=0.01) as assessed by validated Western blot (normalized to myosin heavy chain); the median change from baseline was 3.8%. All patients demonstrated an increase in dystrophin levels over their baseline values." As assessed by mass spectrometry (normalized to filamin C), mean dystrophin levels increased from 0.6% (SD 0.2) of normal at baseline to 4.2% (SD 3.7) of normal by Week 25, with a mean change in dystrophin of 3.7% (SD 3.8) of normal levels (nominal p=0.03, not adjusted for multiple comparisons); the median change from baseline was 1.9%."	"Efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 48 of Part 2. Muscle biopsies were obtained at baseline prior to treatment and at Week 48 of Part 2 in all VYONDYS 53-treated patients (n=25), and were analyzed for dystrophin protein level by Sarepta western blot. Mean dystrophin levels increased from 0.10% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal by Week 48 of Study 1 Part 2, with a mean change in dystrophin of 0.92% (SD 1.01) of normal levels (p <0.001); the median change from baseline was 0.88%."

[51] Viltepso Prescribing Information 3/2021, Section 14 Clinical Studies.
[52] Vyondys 53 Prescribing Information 2/2021, Section 14 Clinical Studies.

65. In addition to the median changes in dystrophin levels reported, there are individual patient results reported. For VILTEPSO, patients experienced a percent change from baseline of 0.69-13.91.[53] For VYONDYS 53, patients experienced a percent change from baseline of 0.01-3.99.[54]

66. Given the different methods used to quantitate the amount of dystrophin produced from treatment of each drug, it is difficult to compare the benefit of each in order to decide which to prescribe. However, since levels were compared from a baseline, it appears that VILTEPSO has median change of 2-4% dystrophin from baseline, versus VYONDYS 53 which is reported to have a median change of 0.88%, [redacted] Since dystrophin production was considered a surrogate marker by the FDA for the drugs' approval, in my opinion and evaluation, these differences would favor starting VILTEPSO over VYONDYS 53. I understand there have been no head-to-head studies of these two products, thus physicians must make their own assessment of the currently available information. Based on the sales of VILTEPSO, other physicians have reached a similar conclusion and have elected to prescribe VILTEPSO

67. I evaluated information, including from the sources noted above in making prescribing decisions related to exon skipping therapies for DMD patients, including exon 53 skipping therapies. In selecting between the exon 53 skipping therapies, I elected to recommend VILTEPSO over VYONDYS 53. Specifically, in my practice, I have had the experience of considering what exon 53 therapy would be appropriate to prescribe to an exon 53 amenable DMD patient. On September 28, 2022, this patient presented at the clinic with elevated CPK and developmental delay. Genetic testing was ordered and confirmed DMD with mutation amenable to exon 53 skipping. As part of this patient's treatment, I considered starting corticosteroids and an exon 53 skipper. I discussed possible treatment options with the family, and we agreed to start VILTEPSO at least because of the finding of [redacted] percentage of dystrophin from baseline found in the original studies and the functional data available to date. Other clinicians may have [redacted] come to the conclusion to recommend VILTEPSO or VYONDYS 53 based on their own evaluations.[55] Because the dystrophin data was not obtained in the same way in the VILTEPSO and VYONDYS 53 studies, we do not know how elevated a dystrophin level has to be to make a functional difference.

68. But for VYONDYS 53 being available in the market, VILTEPSO would have been a suitable therapeutic substitute given the indications and usage are the same, the risk profile is similar and both demonstrated an increase in dystrophin production as the primary endpoint.

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[53] Viltepso Prescribing Information 3/2021, Section 14 Clinical Studies, Table 2.
[54] Vyondys 53 Prescribing Information 2/2021, Section 14 Clinical Studies.
[55] I understand that since the launch of Viltepso, according to Sarepta, about [redacted] of patients are now using Viltepso as compared to [redacted] Vyondys 53; Sehinovych Depo. at pp. 167-168. I also understand that Sarepta has observed patients [redacted]. SRPT-VYDS-0219874.

EXHIBIT D

[redacted]

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (GBW)
SAREPTA THERAPEUTICS, INC., Defendant and Counter-Plaintiff, and UNIVERSITY OF WESTERN AUSTRALIA, Counter-Plaintiff v. NIPPON SHINYAKU CO., LTD., Plaintiff and Counter-Defendant and NS PHARMA, INC., Counter-Defendant.	

REPLY TECHNICAL EXPERT REPORT OF JONATHAN STROBER, M.D.

[redacted]

IV. RESPONSE TO OPINIONS OF SAREPTA'S CONSULTANTS REGARDING THE NIPPON SHINYAKU PATENTS

A. Relative Levels of Dystrophin Induced by Administration of VYONDYS 53 and VILTEPSO

6. Dr. Nelson opines, "it is not possible to make any express or implicit comparison between dystrophin levels induced by administration of Vyondys 53 and Viltepso."[1]

7. I understand and agree that there have been no head-to-head studies between VYONDYS 53 and VILTEPSO [2], and the clinical trial data for the VYONDYS 53 and VILTEPSO studies report (amongst other data) Western blot data reflecting dystrophin levels that were conducted in different labs, at different times, using different methodologies.[3]

8. However, clinicians can and do use all information available to them – including the published studies -- to make prescribing decisions, even if a head-to-head study does not exist such that a direct, quantitative comparison between the study results from the VYONDYS 53 and VILTEPSO clinical trials or superiority marketing claim cannot be made.[4] In addition to other reported data, the relative change in dystrophin production observed within each study (which includes its own internal controls) is informative. Physicians can and should use all information available to make informed treatment recommendations for each patient considering their individual needs.

9. I have reviewed Dr. Nelson's Rebuttal Report Section III.A[5], and maintain my opinion that amongst other information available for these products, the [redacted] change in baseline dystrophin levels following VILTEPSO treatment favors its use over VYONDYS 53.[6]

10. Dr. Nelson suggests quantitative Western blot data are unreliable (e.g., because of baseline levels of dystrophin, lack of dystrophin protein standard, inherent variability in healthy muscle samples or across different muscle groups, use of a standard curve, dystrophin degradation), difficulty of gel separation, fat and fibrotic tissue impacting biopsies).[7] He does not explain how or why each of these examples he cites impacted the relative change in dystrophin levels reported in the VILTEPSO and VYONDYS 53 clinical trials, or how or why these issues would not have been controlled for or commented on in the studies.

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[1] Rebuttal Expert Report of Dr. Stanley Nelson, M.D. (October 9, 2023) and exhibits cited therein ("Nelson Rebuttal Report"); see Section III.A, ¶16.
[2] Nelson Rebuttal Report ¶6; Strober Opening Report ¶66.
[3] Nelson Rebuttal Report ¶11, 13.
[4] It is not uncommon for there not to be head-to-head studies between alternative therapies used to treat the same indication. This is particularly true for therapies approved under the accelerated pathway, and in limited patient populations, such as for DMD. As Dr. Nelson notes, NS does not and cannot yet make a claim of product superiority based on the available information. Nelson Rebuttal Report ¶10.
[5] Nelson Rebuttal Report ¶¶7-8.
[6] Strober Opening Report ¶¶66-67.
[7] Nelson Rebuttal Report ¶12.

[redacted]

a. Dr. Nelson notes that the baseline levels of dystrophin differ between the VILTEPSO and VYONDYS 53 clinical trials but does not explain how or why this would impact the relative fold increase in dystrophin production after each treatment using each assay.[8]

b. Dr. Nelson notes that the VILTEPSO and VYONDYS 53 clinical trials and use a different standard curve but does not explain how or why this would impact the relative fold increase in dystrophin production after each treatment using each assay.[9]

11. While there may be room for improvement in the methods used for measuring dystrophin expression, Western blotting remains a standard test for analyzing dystrophin production. As Dr. Nelson notes, there are other techniques used beyond Western blotting (e.g., immunofluorescence/immunohistochemistry), which are also reported in the clinical study reports that correlate to the reported dystrophin expression in many cases. .

12. Although the details of each manufacturer's Western blotting technique are not disclosed, it is reasonable to presume that each group controlled for known variables to the best of their abilities and reported to the FDA and in manuscripts only reliable data. Based on my understanding of the FDA review process, FDA reviewers would have been critical of data that was not of sufficient quality to base an approval decision. And based on my experience as an author and journal reviewer, reviewers would have been critical of data that was not of sufficient quality to base the results of conclusions set forth in a peer reviewed publication.

13. Further, as Dr. Nelson notes, Sarepta and NS have defined and the FDA has used dystrophin production (as measured by Western blotting) as a primary endpoint for studies evaluating the efficacy of DMD treatments, and thus as a surrogate for potential clinical benefit.[10] While the FDA notes that there can be differences in assay protocols that make results not directly comparable, the FDA does not question the reliability of the technique generally, nor the relative results of samples tested using the same assay protocol.[11] The FDA has determined that the production of dystrophin (in the case of DMD by patients who have genetic defect(s) that prevent the normal production of dystrophin) is a primary endpoint for clinical studies and a surrogate measure indicating the potential for functional benefit of these therapies for these patients.[12]

14. Also, the FDA has presumably reviewed and agreed that the methodologies employed by each manufacturer for detecting dystrophin production are suitably reliable such that the assay is appropriately used to evaluate as a primary endpoint and be potentially predictive of functional benefit.

[8] Nelson Rebuttal Report ¶14.
[9] Nelson Rebuttal Report ¶14.
[10] Nelson Rebuttal Report ¶17, 52.
[11] Nelson Rebuttal Report ¶13.
[12] Nelson Opening Report ¶¶46 and 51 (citing Frank 2020), 54 (citing Servais 2022), 75 (citing Clemens 2020).

[redacted]

15. Since the FDA relies on this information to evaluate the safety and potential efficacy of these products, it is neither uncommon nor unreasonable for physicians to rely on this information in making prescribing decisions.

16. As noted above, what is informative is the relative change in dystrophin production observed within each study, at least because each study includes its own internal controls and because other reported data can be used to contextualize the relative change in dystrophin levels.

17. Dr. Nelson cites an important piece of information that would be considered by physicians--"Although direct comparisons cannot be made across studies, dystrophin levels induced by viltolarsen [redacted]."[13]

18. Study design and methodology. With respect to designing and conducting the Western blotting assays reported in each clinical study, each manufacturer presumably uses great care in the handling of the muscle biopsy samples, isolation and assaying of the dystrophin protein, and validates their assay such that differences in dystrophin are detectable, and powers and statistically analyzes the data in such a way such that a treatment effect can be evaluated. This is especially true given the limited numbers of patients in these clinical trials and the fact that muscle biopsies are painful for the patient. Further, Western blotting methods (even for dystrophin) are well established, having been used for example, in studies evaluating the effectiveness of various steroid treatments in DMD patients.

19. I understand that more detailed information is provided to the FDA in a manufacturer's regulatory applications – Investigational New Drug Application (IND) and Biologics License Application (BLA), while relatively less detailed information is provided in manuscripts describing the clinical trials. Unless a clinician is involved in the clinical trial or submission of the regulatory applications, they would not have access to the detailed information contained in the applications, only the manufacturer's reports of the resulting data.

20. Each clinical trial study for VYONDYS 53 and VILTEPSO included muscle biopsies before and after treatment, such that the impact of treatment in each patient could be evaluated in the same study, and for the Western blot analysis – the patient's own biopsies could be evaluated in the same lab, at the same time, using the same methods.

21. By way of example, for the VYONDYS 53 clinical trials, the muscle biopsies and assays were described as follows: "Muscle biopsies were obtained at baseline prior to treatment and at Week 48 in all 25 Vyondys 53®-treated patients and the dystrophin protein level was analyzed by Western blot."; "Muscle biopsy specimens were collected from one biceps brachii muscle at baseline and from the contralateral muscle at week 48 using an optimized,

[13] Nelson Rebuttal Report ¶7, citing Clemens 2020 at 989.

[redacted]

standardized surgical procedure developed to avoid technical issues previously experienced during other studies in the field."[14]

22. By way of example, for the VILTEPSO clinical trials, the muscle biopsies and assays were described as follows: "dystrophin protein production measured by Western blot in participants' biceps muscles"; "Study 201 demonstrated significant increases in dystrophin content in the treatment group's week 25 posttreatment biopsies as measured by Western blot ."[15]

23. Evaluating Western blot data in the context of additional data from the clinical study reports. As I and Dr. Nelson previously noted[16], in additional to the Western blot data, other secondary endpoints and data are provided in each clinical study report. Dr. Nelson's Opening report indicates that which there was no significant functional benefit of VYONDYS 53 treatment, there were functional benefits reported for VILTEPSO.[17] As I have said, we do not know how elevated dystrophin levels must be to have a functional benefit[18], however, the relative change in dystrophin production following VILTEPSO and VYONDYS 53 treatments may correlate to relative functional benefit.

24. Dr. Nelson does not say if or how the clinical trial information relating to VILTEPSO and VYONDYS 53 is used by clinicians to make prescribing decisions, nor how patients he observed appeared to have benefitted from exon 53 skipping therapies.[19] He only states that "the dystrophin numbers… cannot be meaningfully compared in the simplistic way that Dr. Strober compares them." As noted, physicians view these numbers in the context of all of the available information and in view of our patient's needs.

25. Further, as noted in my Opening Report, I understand that insurers (payors) have made similar comparisons based on dossiers presented by each Sarepta and NS (which do not include head-to-head studies), in deciding whether to prioritize one therapy over another.[20]

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[14] Nelson Opening Report, ¶¶42, 45 (citing Frank 2020), 56 (citing Servais 2022); *see also* 53 discussing the "validated methodology"; 60 (dystrophin expression to be used as a secondary endpoint in the Phase III trial). More specifically, Frank 2020 states, "Muscle biopsy specimens were collected from one biceps brachii muscle at baseline and from the contralateral muscle at week 48 of part 2 using an optimized, standardized surgical procedure developed to avoid technical issues previously experienced during other studies in the field.20 For each biopsy surgery, 2 pieces of muscle (samples A and B) were excised, allocated, and analyzed separately. Patients in the untreated group did not have muscle biopsies and were not included in dystrophin assessments." Strober Opening Report, ¶52, fn 37.

[15] Nelson Opening Report, ¶¶142, 144 (Clemens 2020, citing the study protocol NCT0274071 which states: "All patients will undergo a muscle biopsy of the bicep at baseline and a second muscle biopsy at Week 24." https://clinicaltrials.gov/study/NCT02740972, last accessed Oct. 25, 2023); Strober Opening Report, ¶52, fn 36.

[16] Paragraph 11, *supra* and Strober Opening Report, ¶52 (techniques described in cited articles, including immunohistochemistry, RT-PCR); Nelson Opening Report, Sections VI (Sarepta's Vyondys 53) and IX (NS' Viltepso).

[17] Nelson Opening Report. Compare ¶¶57-59 ("possible functional benefit", "potential functional benefits").

[18] Strober Opening Report ¶67.

[19] Nelson Rebuttal Report ¶17.

[20] Strober Opening Report ¶46.

[redacted]

26. In conclusion, while it is not possible to directly compare the numerical values of the dystrophin production following treatment of VYONDYS 53 and VILTEPSO it is possible to make a comparison of the relative change within each study and/or an implicit comparison between dystrophin levels induced by administration of VYONDYS 53 and VILTEPSO in the context of other data from the studies.

B. Long-Felt Need and Praise for the alleged inventions of the Wilton Patents

27. Dr. Nelson sets forth information suggestive that at the time the "Wilton Patents" were filed in 2005, there was a long felt need for this technology and the technology has received praise since that time.[21] I understand this information may relate to the validity of the Sarepta patents, as well as the NS patents.[22]

28. I understand that the "Wilton Patents" refer to the patents asserted by Sarepta against NS's VILTEPSO product in this litigation[23], and that Sarepta contends that its VYONDYS 53 product practices the Wilton patents.[24]

29. I understand the Wilton Patents include the same specification (which I understand includes the description of the field, background art, disclosure of the invention, figures, and examples), but have different claims. I understand that the Wilton Patents relate to an antisense molecule capable of binding to a selected target site to induce exon skipping in the dystrophin gene.

a. U.S. Patent No. 9,994,851.[25]

(i) Claim 1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

(ii) Claim 2. A pharmaceutical composition comprising: (i) an antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin

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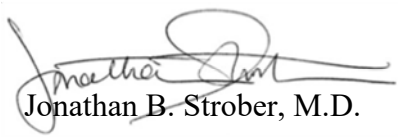
[21] Nelson Rebuttal Report, Section III.B. at ¶¶18-23.
[22] Nelson Rebuttal Report ¶18; Strober Opening Report ¶7.
[23] I understand that Sarepta contends that VILTEPSO practices one or more claims of the Wilton Patents and that NS denies these allegations.
[24] Nelson Rebuttal Report ¶22; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations for VYONDYS 53. (https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=211970&Appl_type=N (last accessed Oct 24, 2023), listing in Patent and Exclusivity Information: Patent Nos. 9024007, **9994851**, **10227590**, **10266827**, 10421966, 10968450, 10995337 and RE47691 (emphasizing Sarepta's asserted patents)
[25] https://patentimages.storage.googleapis.com/f6/e6/71/0445eb558ccb99/US9994851.pdf (last accessed Oct. 24, 2023).

[redacted]

44. As stated in my opening report, VYONDYS 53 was approved December 12, 2019 and VILTEPSO was approved August 12, 2020—eight months later. I disagree with Mr. Jarosz's premise that most or all of the exon 53 amenable patients who were eligible for VYONDYS 53 in August 12, 2020 would have [redacted] at least because [the disease does not progress so quickly that if there were an eight month delay that a patient's condition would have changed substantially in that time. In any event, in my experience such as with patients being treated with EXONDYS 51 and AMONDYS 45, even non-ambulatory patients are treatable and so would not have been excluded from the treatable patient population. Further, the population of DMD patents is relatively predictable in that for the few patients [redacted]

October 27, 2023



Jonathan B. Strober, M.D.

EXHIBIT E

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	**C.A. No. 21-1015-JLH** [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

SUPPLEMENTAL OPENING EXPERT REPORT OF JOHN C. JAROSZ

April 12, 2024

SUPPLEMENTAL TAB 8

SAREPTA - VYONDYS 53®
MONTHLY U.S. SALES
JULY 2019 – FEBRUARY 2024

		2023												
		Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Total
		[BA]	[BB]	[BC]	[BD]	[BE]	[BF]	[BG]	[BH]	[BI]	[BJ]	[BK]	[BL]	[BM]
	Vials													
[1]	Vials (Paid)	[redacted]												
[2]	Vials (Free)													
[3]	Vials (Total)													
	Sales													
[4]	Gross Sales													
[5]	340B													
[6]	Medicaid													
[7]	Tricare													
[8]	Data/Dist													
[9]	Copay													
[10]	Prompt Pay													
[11]	**Net Sales**													
	Cost of Sales													
[12]	Product Cost of Goods Sold													
[13]	Amortization COGS													
[14]	Other COGS													
[15]	Excess & Obsolescence													
[16]	**Total Cost of Sales**													
[17]	*% of Net Sales*													
[18]	**Gross Profit**													
[19]	*% of Net Sales*													
[20]	Commercial Expenses													
[21]	**Commercial Profit**													
[22]	*% of Net Sales*													
[23]	Vyondys R&D													
[24]	R&D Allocation													
[25]	G&A Allocation													
[26]	**Total Operating Expenses**													
[27]	*% of Net Sales*													
[28]	**Fully Loaded Profit**													
[29]	*% of Net Sales*													
	Per Paid Vial													
[30]	Gross Sales													
[31]	Net Sales													
[32]	Cost of Sales													
[33]	Gross Profit													
[34]	Operating Expenses													
[35]	Fully Loaded Profit													

SUPPLEMENTAL TAB 8

SAREPTA - VYONDYS 53®
MONTHLY U.S. SALES
JULY 2019 – FEBRUARY 2024

		2024			Total
		Jan.	Feb.	Total	Jul. 2019 – Feb. 2024
		[BN]	[BO]	[BP]	[BQ]
	Vials				
[1]	Vials (Paid)	[redacted]			
[2]	Vials (Free)				
[3]	Vials (Total)				
	Sales				
[4]	Gross Sales				
[5]	340B				
[6]	Medicaid				
[7]	Tricare				
[8]	Data/Dist				
[9]	Copay				
[10]	Prompt Pay				
[11]	**Net Sales**				
	Cost of Sales				
[12]	Product Cost of Goods Sold				
[13]	Amortization COGS				
[14]	Other COGS				
[15]	Excess & Obsolescence				
[16]	**Total Cost of Sales**				
[17]	*% of Net Sales*				
[18]	**Gross Profit**				
[19]	*% of Net Sales*				
[20]	Commercial Expenses				
[21]	**Commercial Profit**				
[22]	*% of Net Sales*				
[23]	Vyondys R&D				
[24]	R&D Allocation				
[25]	G&A Allocation				
[26]	**Total Operating Expenses**				
[27]	*% of Net Sales*				
[28]	**Fully Loaded Profit**				
[29]	*% of Net Sales*				
	Per Paid Vial				
[30]	Gross Sales				
[31]	Net Sales				
[32]	Cost of Sales				
[33]	Gross Profit				
[34]	Operating Expenses				
[35]	Fully Loaded Profit				

SUPPLEMENTAL TAB 10

NS - VILTEPSO®
U.S. MONTHLY SALES
AUGUST 2020 – FEBRUARY 2024

		2023												
		Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.	Total
		[AN]	[AO]	[AP]	[AQ]	[AR]	[AS]	[AT]	[AU]	[AV]	[AW]	[AX]	[AY]	[AZ]
	Vials (U.S.)													
[1]	Vials (U.S.)	[redacted]												
	Sales (U.S.)													
[2]	Gross Sales													
[3]	Returns													
[4]	Rebates													
[5]	Medicaid Rebates													
[6]	Tricare Rebates													
[7]	Copay													
[8]	Prompt Pay Discount													
[9]	Other Returns, Rebates, Fees, and Discoun													
[10]	Federal Chargeback													
[11]	**Net Sales (U.S.)**													
	Cost of Sales (U.S.)													
[12]	Cost of Goods Sold													
[13]	Logistics													
[14]	Packaging													
[15]	**Total Cost of Sales**													
[16]	*% of Net Sales*													
[17]	**Gross Profit (U.S.)**													
[18]	*% of Net Sales*													
	Expenses (U.S.)													
[19]	Total Personal Expenses													
[20]	Operating Expenses - Consulting													
[21]	Operating Expenses - Other													
[22]	**Total Expenses (U.S.)**													
[23]	*% of Net Sales*													
[24]	**Net Income From Operations (U.S.)**													
[25]	*% of Net Sales*													
	Per Vial (U.S.)													
[26]	Gross Sales													
[27]	Net Sales													
[28]	Cost of Sales													
[29]	Gross Profit													
[30]	Expenses													
[31]	Operating Profit													

SUPPLEMENTAL TAB 10

NS - VILTEPSO®
U.S. MONTHLY SALES
AUGUST 2020 – FEBRUARY 2024

		2024			Total
		Jan.	Feb.	Total	Aug. 2020 – Feb. 2024
		[BA]	[BB]	[BC]	[BD]
	Vials (U.S.)				
[1]	Vials (U.S.)	[redacted]			
	Sales (U.S.)				
[2]	Gross Sales				
[3]	Returns				
[4]	Rebates				
[5]	Medicaid Rebates				
[6]	Tricare Rebates				
[7]	Copay				
[8]	Prompt Pay Discount				
[9]	Other Returns, Rebates, Fees, and D				
[10]	Federal Chargeback				
[11]	**Net Sales (U.S.)**				
	Cost of Sales (U.S.)				
[12]	Cost of Goods Sold				
[13]	Logistics				
[14]	Packaging				
[15]	**Total Cost of Sales**				
[16]	*% of Net Sales*				
[17]	**Gross Profit (U.S.)**				
[18]	*% of Net Sales*				
	Expenses (U.S.)				
[19]	Total Personal Expenses				
[20]	Operating Expenses - Consulting				
[21]	Operating Expenses - Other				
[22]	**Total Expenses (U.S.)**				
[23]	*% of Net Sales*				
[24]	**Net Income From Operations (U.S.)**				
[25]	*% of Net Sales*				
	Per Vial (U.S.)				
[26]	Gross Sales				
[27]	Net Sales				
[28]	Cost of Sales				
[29]	Gross Profit				
[30]	Expenses				
[31]	Operating Profit				

EXHIBIT F

[redacted]

Transcript of Stephen Sudovar, Designated Representative, and Individually

Date: July 18, 2023
Case: Nippon Shinyaku Co., Ltd. -v- Sarepta Therapeutics, Inc.

Planet Depos
Phone: 888.433.3767
Email: transcripts@planetdepos.com
www.planetdepos.com

Q With disclaimers, right? 11:12:10
A I'm not sure what you mean by disclaimers. 11:12:14
Q Are you allowed to create marketing 11:12:24
materials that directly compare Viltepso and 11:12:27
Vyondys? 11:12:31
A No. 11:12:31
Q Why not? 11:12:32
MS. VENEGAS: Objection to form to the 11:12:34
extent it calls for an expert or legal conclusion 11:12:37
or opinion. 11:12:40
A There are no head-to-head studies. 11:12:41
Q Does NS Pharma plan any head-to-head 11:12:44
studies? 11:12:49
MS. VENEGAS: Objection to form. 11:12:49
A I have no idea. 11:12:50
MS. VENEGAS: Sorry, let me object. 11:12:51
A Please. 11:12:53
MS. VENEGAS: Objection to form. Outside 11:12:53
the scope. 11:12:54
You can answer as an individual if you 11:12:55
know. 11:12:57
A I did not. 11:12:57
MR. O'QUINN: Let's take a break. 11:13:00
THE VIDEOGRAPHER: We are going off the 11:13:02
record. The time is 11:13 a.m. 11:13:03

the extent it calls for a legal or expert opinion. 11:41:30
A I would require guidance from our 11:41:33
regulatory and legal. 11:41:38
Q When we were discussing before the break, 11:41:44
you said that NS Pharma was approved to present 11:41:47
functional data, but it can only do so with this 11:41:51
disclaimer next to it, right? 11:41:58
MS. VENEGAS: Objection to the form, and 11:41:59
to the extent it mischaracterizes the document. 11:42:01
You can answer. 11:42:03
A I would require guidance from regulatory 11:42:10
and legal. 11:42:14
Q If we look on the next page, there is 11:42:14
secondary endpoints listed in a table with some 11:42:18
functional tests. They include time to stand, 11:42:24
time to climb four stairs, time to run/walk ten 11:42:28
meters, six-minute walk test and the north star 11:42:33
ambulatory assessment, right? 11:42:36
A Yes. 11:42:40
Q And there's functional data presented for 11:42:40
Viltepso in this table, right? 11:42:46
A Yes. 11:42:48
Q This data is not presented as a comparison 11:42:54
to Vyondys, correct? 11:42:58
A That's correct. 11:43:02

Q And NS Pharma cannot make that comparison, correct? 11:43:03 11:43:10

MS. VENEGAS: Objection to form to the extent it calls for a legal or expert opinion. 11:43:10 11:43:13

A I'd say no. 11:43:15

Q The functional data is not presented as a comparison to placebo from any clinical trial involving Viltepso, correct? 11:43:19 11:43:27 11:43:32

A That's correct. 11:43:37

Q NS Pharma does not have that data, correct? 11:43:38 11:43:42

MS. VENEGAS: Objection to form. And also outside the scope. 11:43:43 11:43:45

You can answer as an individual if you know. 11:43:47 11:43:49

A I do not. 11:43:50

Q If you can go with me to the Page 13 out of 22, please. At the bottom of that page there is a heading: "Long-term data and safety, four-year, long-term open-label functional assessment data." 11:43:51 11:44:08 11:44:18 11:44:22 11:44:25

Do you see that? 11:44:27

A I do. 11:44:27

Q You described that data during your testimony earlier this morning, correct? 11:44:28 11:44:30

EXHIBIT G

19 June 2019

Viltolarsen (NS-065/NCNP-01) FAQ

Introduction: Please refer to the answers below as you answer questions posed by study participants and other members of the Duchenne muscular dystrophy (DMD) community. These answers have been reviewed and approved by NS Pharma and Nippon Shinyaku for this use only. Please do not distribute nor publish this document nor its contents outside of the study team.

If you feel uncomfortable answering certain questions included in this document, or if you would like more help with certain topics, please email dmdresearch@nspharma.com to contact the Medical Affairs for this study.

Presentation slides which were recently used at webinars or conferences are available on the NS Pharma website (www.nspharma.com) by clicking the “Healthcare Professional” button, for healthcare professionals.

F. Japan Phase 1/2 and North America Phase 2 Results: Safety

1. **What were the safety results for North America and Japan studies?**

   Answer: We observed safety and tolerability up to 80 mg/kg doses in both studies.

2. **Do you have any comments on renal (kidney) safety?**

   Answer: interim safety data was presented so far. However, since the safety and efficacy of viltolarsen has not been established by any Health Authorities, and it is not approved for the treatment of DMD in US or globally, we are not ready to make any comments. (We have seen some elevation in a renal marker in Japanese study. The interim safety data is available in Japanese PI/PII study poster at WMS last year and Investigator Initiated Trial article.)

G. Japan Phase 1/2 and North America Phase 2 Results: Comparison to Other Results

1. **What are the differences observed between golodirsen (SPR-4053) and viltolarsen (NS-065/NCNP-01) in terms of the dystrophin production? What could be possible reasons to explain this?**

   Answer: We cannot make any direct comparisons of Viltolarsen to other investigational therapies for DMD, as there have been no head-to-head studies.

2. **How is golodirsen different from viltolarsen (NS-065/NCNP-01)?**

   Answer: We cannot make any direct comparisons of Viltolarsen to other investigational therapies for DMD, as there have been no head-to-head studies.

3. **What do you think about the differences observed between Sarepta's AAVrh74.MHCK7 micro-dystrophin gene therapy disclosed on Jun 19, 2018 and NS-065 Phase 2 in terms of the dystrophin production?**

   Answer: We cannot make any direct comparisons between the two studies.

H. North America Phase 2 Results: Sharing Individual Dystrophin Data with Investigators and Patients/Patient Families

1. **When will you share individual dystrophin data with investigators? Can investigators share individual dystrophin data with families?**

   Answer: Sharing the individual data could bias the clinical function tests being done as part of the extension (202) study. We will inform the investigators when we can share

EXHIBIT H

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Research Report

Long-Term Functional Efficacy and Safety of Viltolarsen in Patients with Duchenne Muscular Dystrophy

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Abstract.
Background: Duchenne muscular dystrophy (DMD) is a rare, genetic disease caused by mutations in the DMD gene resulting in an absence of functional dystrophin protein. Viltolarsen, an exon 53 skipping therapy, has been shown to increase endogenous dystrophin levels. Herein, long-term (>2 years) functional outcomes in viltolarsen treated patients were compared to a matched historical control group.
Objective: To evaluate long-term efficacy and safety of the anti-sense oligonucleotide viltolarsen in the treatment of patients with DMD amenable to exon 53 skipping therapy.
Methods: This trial (NCT03167255) is the extension of a previously published 24-week trial in North America (NCT02740972) that examined dystrophin levels, timed function tests compared to a matched historical control group (Cooperative International Neuromuscular Research Group Duchenne Natural History Study, CINRG DNHS), and safety in boys 4 to < 10 years ($N = 16$) with DMD amenable to exon 53 skipping who were treated with viltolarsen. Both groups were

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treated with glucocorticoids. All 16 participants elected to enroll in this long-term trial (up to 192 weeks) to continue evaluation of motor function and safety.

Results: Time to stand from supine and time to run/walk 10 meters showed stabilization from baseline through week 109 for viltolarsen-treated participants whereas the historical control group showed decline (statistically significant differences for multiple timepoints). Safety was similar to that observed in the previous 24-week trial, which was predominantly mild. There have been no treatment-related serious adverse events and no discontinuations.

Conclusions: Based on these results at over 2 years, viltolarsen can be a new treatment option for patients with DMD amenable to exon 53 skipping.

Keywords: Duchenne muscular dystrophy, dystrophin, viltepso, viltolarsen, exon skipping, clinical efficacy

INTRODUCTION

Duchenne muscular dystrophy (DMD), an X-linked recessive disorder, affects approximately 1 : 3600 to 1 : 9300 male newborns worldwide [1]. In patients with DMD, loss-of-function variants in the *DMD* gene result in an absence of functional dystrophin protein, leading to progressive weakness and degeneration of skeletal muscle [2, 3], cardiac dysfunction, respiratory failure, and, ultimately, premature death [2, 4]. However, individuals with *DMD* mutations who have low levels of normal dystrophin protein from birth [5, 6] and those with in-frame deletions that result in the production of truncated dystrophin protein [7] may exhibit a milder, slower-progressing, and less severe disease [5, 7].

Exon skipping therapies developed for the treatment of DMD have the potential to increase levels of functional dystrophin. The exon skipping approach aims to shift the reading frame to convert a *DMD* out-of-frame variant to an in-frame, Becker muscular dystrophy-like deletion, leading to an endogenously produced, internally shortened version of the dystrophin protein that retains essential functional portions [7–9]. Viltolarsen is a phosphorodiamidate morpholino oligomer/antisense oligonucleotide designed to treat DMD in patients with a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping [9, 10]. The exon 53 skipping approach could be therapeutic in approximately 8% to 10% of patients with DMD caused by an out-of-frame deletion, including, but not limited to, those with deletions such as exons 43-52, 45-52, 47-52, 48-52, 49-52, 50-52, or 52 alone [3, 11, 12].

An initial Phase 2, two period, randomized, dose-finding trial consisted of a 4-week double-blinded, placebo-controlled period for safety of viltolarsen followed by a 20-week open-label period to evaluate the efficacy, safety, and tolerability of viltolarsen (40 or 80 mg/kg/week) in boys 4 to < 10 years of age with DMD ($N = 16$) amenable to exon 53 skipping [13]. Participants were ambulatory and could complete motor function assessments at screening. Participants had been treated with a stable dose of glucocorticoids for at least 3 months prior to enrollment and were expected to remain on the stable dose for the duration of the study. Treatment with viltolarsen resulted in significant increases in dystrophin production, as assessed by Western blot after 20 to 24 weeks of treatment (80 mg/kg/wk: 5.9% of normal at week 25 vs 0.6% at baseline) [13]. This initial Phase 2 study also included timed function tests, designed to provide evidence of treatment-related improvements in clinical functioning when compared with DMD natural history controls provided by the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS), who were matched for age, geographic location, ambulatory ability at baseline, and glucocorticoid treatment. The viltolarsen cohort demonstrated significant improvements from baseline on timed function tests, including time to stand from supine (TTSTAND), time to run/walk 10 meters (TTRW), and 6-minute walk test (6MWT) [13]. Adverse events (AEs) were predominantly mild; no treatment-related serious AEs were reported, and no participants discontinued from the study. Based on these data, viltolarsen received accelerated approval for the treatment of DMD patients with mutations amenable to exon 53 skipping in the United States and Japan [14, 15].

At the conclusion of the Phase 2 study, participants were given the opportunity to enroll in the long-term extension (LTE) study (NCT03167255), the primary objective of which was to evaluate the clinical efficacy and safety of viltolarsen over a longer period of time (up to an additional 192 weeks) [16]. All participants elected to continue in the LTE study [17]. Here, we present results at 109 weeks (approximately 2 years) from the open-label LTE study of the original

16 participants enrolled in the North American study [17, 18].

MATERIALS AND METHODS

As previously described, participants for the initial Phase 2 study (NCT02740972) were recruited from 6 sites in North America (UC Davis (Sacramento, California); Lurie Children's Hospital (Chicago, Illinois); Washington University in St. Louis (St. Louis, Missouri); Duke University Medical Center (Durham, North Carolina); Children's Hospital of Richmond at VCU (Richmond, Virginia); Alberta Children's Hospital (Calgary, Alberta, Canada)) [13]. Following completion of this 24-week study, all 16 patients, who were 4 to < 10 years old when enrolled in the initial Phase 2 study, elected to enroll and were followed in the LTE study for up to 192 weeks (NCT03167255). Inclusion criteria again included the requirement for participants to be taking a stable dose of glucocorticoid and to remain on the stable dose for the duration of the study. Treatment for the purpose of dystrophin protein induction or treatment with other investigational drugs after completion of the initial Phase 2 trial were prohibited [16].

Viltolarsen was administered as an IV infusion at a dosage of 40 mg/kg or 80 mg/kg once weekly. All patients received viltolarsen by peripheral venous access during the initial Phase 2 study, and five patients requested placement of a central port at some point during the LTE study.

Efficacy assessments were conducted every 12 weeks [16], and safety was assessed throughout the open-label extension study [19]. [See Fig. 1.] The primary endpoint was TTSTAND; secondary endpoints included TTRW, TTCLIMB, 6MWT, and North Star Ambulatory Assessment (NSAA). Results for the endpoints TTSTAND, TTRW, and TTCLIMB were also converted to velocity, which provides a better and often more reliable accounting of those participants who can no longer perform a test [20]. Clinical assessments were compared to historical controls (CINRG DNHS), who were group-matched for age, geographic location, ambulatory ability

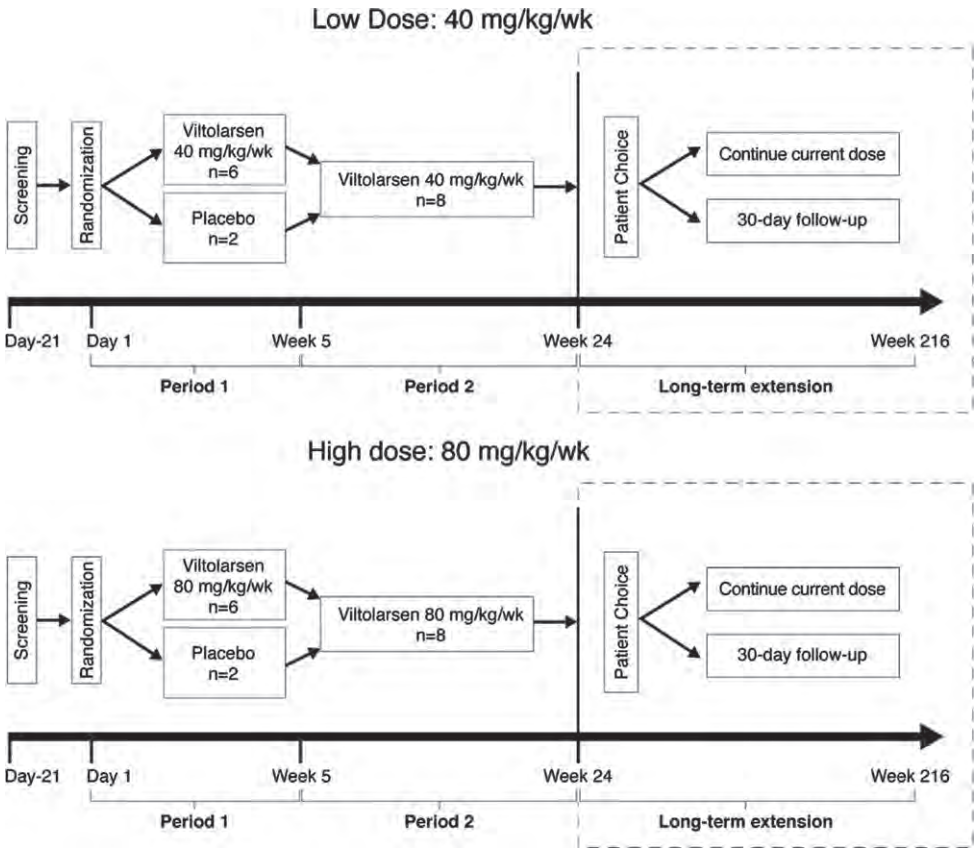

Fig. 1. Design of the Phase 2 and LTE studies. mg, milligrams; kg, kilograms; wk, week.

(defined as all participants being able to perform TTRW, TTSTAND, and TTCLIMB at baseline), and glucocorticoid use. Analysis at 2 years (109 weeks) was selected because the timepoint aligned with sufficient numbers of patients in the CINRG DNHS group, who had functional assessments less frequently than the viltolarsen-treated patients.

The trial protocol was approved by ethics review panels of each participating recruitment center. Prior to any study-related procedures, participants, who were minors, provided written or verbal informed assent appropriate for age and developmental status, and the parent or legal guardian of participants provided written informed consent and/or HIPAA authorization. The trial was performed according to the principles of the Declaration of Helsinki and the Good Clinical Practice regulations. Activities were overseen by an independent data and safety monitoring board.

RESULTS

Participants

All participants ($N = 16$) who completed the Phase 2 study continued participation in the LTE study throughout the period of this report. Most participants (15/16) were white; one was Asian. Their mean age (range) of enrollment in the initial Phase 2 study was 7.4 (4.3, 9.8) years. For this LTE study, participants continued therapy according to their previously assigned viltolarsen dose cohort (low-dose [40 mg/kg per week, $n = 8$] or high-dose [80 mg/kg per week, $n = 8$]). Overall, baseline characteristics between participants in the 2 dose cohorts were balanced. Participants in the external comparator group, whose data were drawn from the CINRG DNHS, were group-matched to the viltolarsen-treated participants (see Methods and Table 1). Nine patients in the CINRG DNHS comparator group had DMD amenable to exon 53 skipping and 56 had DMD with non–exon 53 skipping mutations, excluding patients with deletion of exons 3–7 or gene deletions amenable to exon skipping of exon 44, as these mutation groups have a milder disease progression [13, 19].

Efficacy outcomes

Timed function tests and muscle strength assessments were used to measure disease progression. Data for the primary efficacy endpoint of time to stand from supine (TTSTAND) indicate that function was maintained over 109 weeks in participants treated with viltolarsen, whereas the CINRG DNHS group experienced functional decline (Fig. 2 and Table 2). Improvements were significant at timepoints 73 and 109 weeks for TTSTAND (seconds) and at all timepoints for TTSTAND (velocity). Change from baseline in the secondary efficacy endpoint of TTRW likewise indicated maintenance of function through week 109 in participants treated with viltolarsen versus functional decline in the historical control group (Fig. 3 and Table 2), with significant differences shown at all timepoints after 37 weeks for TTRW (seconds) and at all timepoints for TTRW (velocity). Although TTCLIMB (seconds) and TTCLIMB (velocity) showed numerical improvement at all timepoints, TTCLIMB (seconds) was not significantly different from the control group, and TTCLIMB (velocity) was significantly different from the control group only at 73 weeks (viltolarsen change from baseline [CFB]: 0.05 task/s [SE 0.03], DNHS CFB: –0.05 task/s [SE 0.02]; $P = 0.0082$).

The secondary efficacy endpoints of 6MWT and NSAA were added late in the study to the

Table 1
Baseline Demographic Characteristics of the Participants Enrolled in the Long-term Extension Study of Viltolarsen and the CINRG DNHS Control Cohort

Characteristics	Viltolarsen cohort, mean (range)			CINRG DNHS control cohort, mean (range)		
	40 mg/kg/week ($n = 8$)	80 mg/kg/week ($n = 8$)	Total ($N = 16$)	Exon 53 amenable controls ($n = 9$)	Non-exon 53 amenable controls ($n = 56$)	Total ($N = 65$)
Age, y	7.5 (4.3, 9.8)	7.2 (4.8, 9.8)	7.4 (4.8, 9.8)	6.3 (4.5, 7.8)	7.2 (4.2, 9.6)	7.1 (4.2, 9.6)
Weight, kg	23.7 (14.9, 30.4)	22.3 (15.5, 35.4)	23.0 (14.9, 35.4)	21.6 (16.6, 28.1)	24.4 (14.8, 38.7)	24.0 (14.8, 38.7)
Height, cm	114.6 (102.5, 123.4)	112.2 (99.4, 127.1)	113.4 (99.4, 127.1)	111.3 (102.2, 122.2)	117.0 (96.1, 135.9)	116.2 (96.1, 135.9)
BMI, mg/kg^2	17.9 (14.2, 20.0)	17.4 (15.4, 21.9)	17.7 (14.2, 21.9)	17.3 (15.5, 21.6)	17.6 (13.9, 22.9)	17.5 (13.9, 22.9)

CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; y, years.

Table 2
Efficacy at Week 109

Efficacy at week 109, change from baseline comparison			
Parameter	Viltolarsen LSM (SE)	DNHS LSM (SE)	Between-group comparison, *P*-value
TTSTAND (seconds)	0.43 (1.077)	4.31 (0.786)	0.0044
TTSTAND (velocity)	0.04 (0.023)	–0.08 (0.015)	<0.0001
TTRW (seconds)	–0.44 (0.464)	1.29 (0.309)	0.0024
TTRW (velocity)	0.23 (0.113)	–0.32 (0.080)	0.0001
TTCLIMB (seconds)	1.02 (0.972)	3.00 (0.690)	0.0992
TTCLIMB (velocity)	0.004 (0.029)	–0.05 (0.020)	0.1578

DNHS, Duchenne Natural History Study; LSM, least-squares mean; SE, standard error; TTCLIMB, time to climb 4 stairs; TTRW, time to run/walk 10 meters; TTSTAND, time to stand from supine. Change from baseline was modeled using a residual maximum likelihood (REML)-based, mixed-model repeated measures analysis with treatment group, week of the visit, and treatment-by-week interaction as factors, and age at study entry for viltolarsen/baseline for DNHS as one covariate, and baseline response as a second covariate.

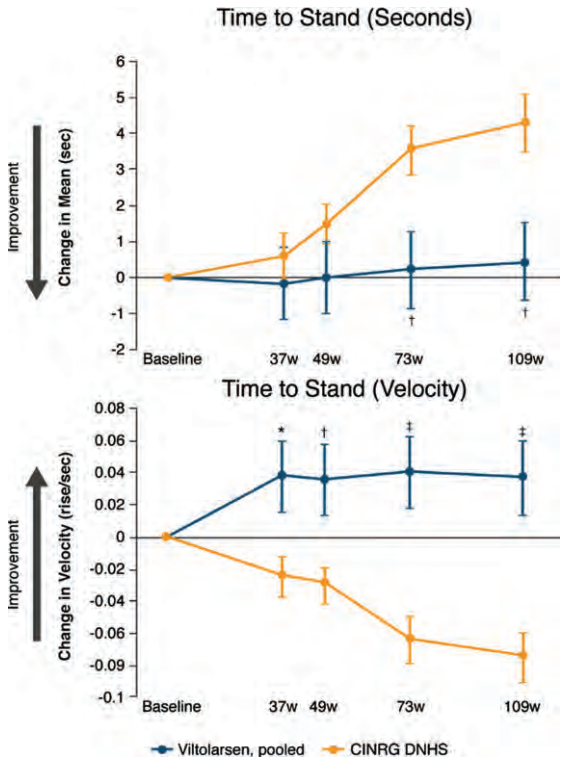

Fig. 2. Change from baseline in time to stand from supine. CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; TTSTAND, time to stand from supine; w, weeks. Calculation of TTSTAND velocity: rise/second. *P<0.05; †P<0.01; ‡$P \leq 0.0001$. Observed sample size for viltolarsen at baseline and for each of the subsequent timepoints on viltolarsen were: $n = 16$, $n = 16$, $n = 15$, $n = 14$, and $n = 14$. Observed sample size for DNHS cohort at baseline and for each of the subsequent timepoints for this cohort were: $n = 65$, $n = 31$, $n = 57$, $n = 24$, $n = 24$ for TTSTAND (seconds); $n = 65$, $n = 31$, $n = 58$, $n = 28$, $n = 28$ for TTSTAND (velocity).

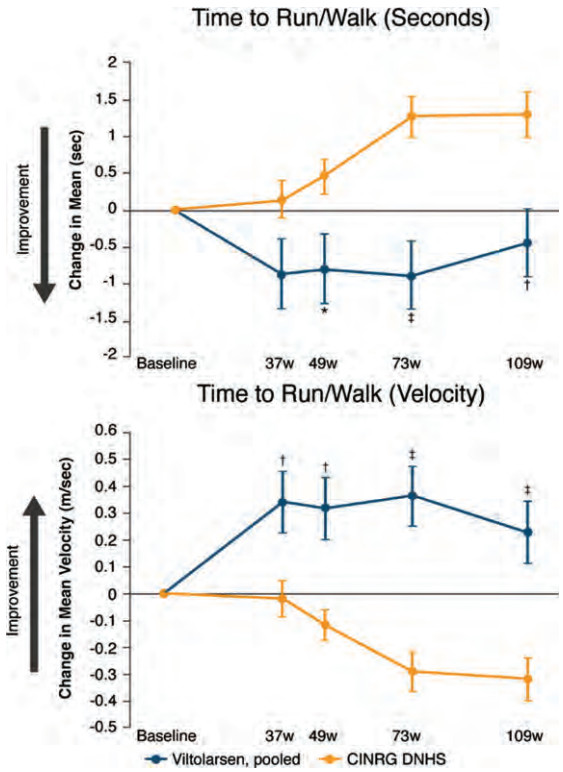

Fig. 3. Change from baseline in time to run/walk 10 meters. CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; TTRW, time to run/walk 10 meters; w, weeks. Calculation of TTRW velocity: meters/second. *P<0.05; †P<0.01; ‡$P \leq 0.0001$. Observed sample size for viltolarsen at baseline and for each of the subsequent timepoints on viltolarsen were: $n = 16$, $n = 16$, $n = 15$, $n = 16$, $n = 16$ for TTRW. Observed sample size for DNHS cohort at baseline and for each of the subsequent timepoints for this cohort were: $n = 65$, $n = 32$, $n = 58$, $n = 28$, $n = 29$ for TTRW (seconds); $n = 65$, $n = 32$, $n = 59$, $n = 29$, $n = 29$ for TTRW (velocity).

CINRG DNHS protocol, and thus the CINRG DNHS comparator group did not have sufficient data on NSAA and 6MWT to adequately compare with the viltolarsen-treated group.

Safety

The overall safety profile of viltolarsen over the LTE study was similar to that observed in the previous 24-week Phase 2 study and was predominantly mild in nature. All 16 participants experienced treatment-emergent adverse events (TEAE) (Table 3). Only one TEAE, an IV infiltration that was considered related to both the study drug and procedure, and graded as mild, occurred in the 80 mg/kg/week viltolarsen group. The most common TEAEs (Table 4), which occurred in ≥ 25% of patients, were cough, nasopharyngitis, insect bite, and rash. There were two serious TEAEs, a lower limb fracture and a case of rhabdomyolysis; both were considered unrelated to viltolarsen treatment. There were no discontinuations due to AEs, and no deaths occurred during the study.

Table 3
Safety Profile of Viltolarsen During the Long-term Extension Study

	Viltolarsen Treatment		
	40 mg/kg/wk ($n = 8$) *n* (%)	80 mg/kg/wk ($n = 8$) *n* (%)	Total ($N = 16$) *n* (%)
Any TEAE*	8 (100)	8 (100)	16 (100)
Any drug-related TEAE	0	1 (12.5)	1 (6.3)
Discontinuation due to TEAEs	0	0	0
Any serious treatment-related TEAE	0	0	0
Death	0	0	0

*TEAE, treatment-emergent adverse event. Note: 80 mg/kg/wk is the FDA-approved dosing regimen for viltolarsen.

Table 4
Patients with Treatment-emergent Adverse Events ≥ 25% Total in Long-term Extension Study

Adverse Events	Viltolarsen Treatment		
	40 mg/kg/wk ($n = 8$) *n* (%)	80 mg/kg/wk ($n = 8$) *n* (%)	Total ($N = 16$) *n* (%)
Cough	5 (62.5)	4 (50.0)	9 (56.3)
Nasopharyngitis	4 (50.0)	4 (50.0)	8 (50.0)
Insect bite	4 (50.0)	2 (25.0)	6 (37.5)
Rash	2 (25.0)	4 (50.0)	6 (37.5)
Fever	2 (25.0)	3 (37.5)	5 (31.3)
Vomiting	3 (37.5)	2 (25.0)	5 (31.3)
Fall	4 (50.0)	0	4 (25.0)
Headache	2 (25.0)	2 (25.0)	4 (25.0)
Influenza	3 (37.5)	1 (12.5)	4 (25.0)
Nasal congestion	3 (37.5)	1 (12.5)	4 (25.0)

Note: 80 mg/kg/wk is the FDA-approved dosing regimen for viltolarsen.

DISCUSSION

We report here that the effects of viltolarsen on timed function tests were maintained over 2 years in this analysis of data from the long-term extension study, compared to a decline in the DNHS historical control group that was matched on key factors such as age, treatment with corticosteroids, ambulatory ability (all participants were required to perform TTRW, TTSTAND, and TTCLIMB at baseline), and geographic location. The present findings represent the first published long-term functional data for viltolarsen therapy used in the treatment of patients with DMD who were 4 to < 10 years of age, ambulant, and taking glucocorticoids at baseline [13]. The safety profile of viltolarsen over 2 years was also similar to that observed in the 24-week Phase 2 trial. This analysis at the 2-year mark suggests clinically relevant motor function was maintained and supports the safety profile of viltolarsen.

Long-term data on the use of FDA-approved DMD therapies are beginning to emerge. A recent paper by Servais and colleagues found that golodirsen treatment in DMD patients ($n = 25$, mean age 8.4 years) amenable to exon 53 skipping did not significantly reduce loss of ambulation, 6MWT, or forced vital capacity evaluations at 3 years relative to external controls [21]. Viltolarsen (presented here) and golodirsen target the same *DMD* gene exon 53. For a different exon-specific drug, two studies evaluated eteplirsen over a period of 3 to 4 years. Mendell and colleagues assessed 6MWT and pulmonary function in exon 51 skip-amenable patients compared with patient-level control data from the Italian DMD Registry and found that eteplirsen ($n = 13$, mean age 9.3 years) treatment provided a significant benefit compared with the historical controls, and pulmonary function remained stable [22]. Similarly, Kinane and colleagues found that eteplirsen treatment attenuated respiratory decline compared with United Dystrophinopathy Project controls over 216 weeks [23].

Limitations

DMD is a rare disease, and only 8%–10% of DMD patients have a variant amenable to exon 53 skipping [3]. While the small sample size ($N = 16$) represents

a limitation of this study, both the study design and sample size are consistent with other studies investigating potential approaches to treatment for this patient population [21–24]. An additional limitation is the use of an historical control group (group-level matched) in this study, rather than a placebo arm. The use of an historical control group, although less rigorous than a randomized, placebo-controlled study design, is appropriate for a Phase 2 trial in a rare disease with a surrogate primary outcome. However, an analysis of the consistency of change in 6-minute walk distance in DMD using group-matched DMD natural history data from 5 separate natural history datasets found that external controls were not different from placebo controls drawn from placebo datasets included in 6 randomized, blinded DMD treatment studies encompassing 4 sets of eligibility criteria [25]. While this study did not use patient-level matching due to the small patient population size in the DMD historical control group; it used group-level matching, which included age, geographic location, ambulatory ability, and glucocorticoid use. To confirm the clinical findings, a Phase 3 randomized, double-blind, placebo-controlled, multi-center study (NCT04060199; RACER53) to assess the efficacy and safety of viltolarsen in boys with DMD who are able to walk independently without assistive devices is being conducted [26].

CONCLUSIONS

Using timed function tests as markers of clinical efficacy, the effects of viltolarsen were maintained in this long-term study over 2 years, compared to a decline in the DMD historical control group that was matched on key factors such as age, ambulatory ability, and glucocorticoid treatment. Further, the safety profile of viltolarsen over this long-term study was mild and similar to that observed in the initial 24-week Phase 2 study. Based on the efficacy and safety results of this Phase 2 long-term extension study, we consider that treatment with viltolarsen offers an important option for patients with DMD with mutations that are amenable to exon 53 skipping.

ACKNOWLEDGMENTS

The authors thank all study participants and their families, as well as the study team members, at participating Cooperative International Neuromuscular Research Group (CINRG) sites for assistance in collecting and managing the data. The authors are grateful to Robert Crozier, PhD, and Leslie Magnus, MD, of NS Pharma, Inc., for discussions and a critical reading of the manuscript.

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Writing and editorial support were provided by Marilyn G. Stearns, MD; and Steven D. Stockton, Jr., MS, PhD; from PRI Healthcare Solutions, and were funded by NS Pharma.

AUTHOR CONTRIBUTIONS

1. Contributed to study conception and design: P.C., T.N., E.H.
2. Analyzed and interpreted data: P.C., V.R., A.C., A.H., J.M., C.M., E.S., C.Z., T.N., E.H.
3. Drafted and reviewed the final publication: P.C., V.R., A.C., A.H., J.M., C.M., E.S., C.Z., T.N., E.H.

The CINRG DNHS Investigators contributed to CINRG DNHS data collection. Please see Supplementary Table for the investigator group's members and affiliations.

CONFLICTS OF INTEREST

a. Dr Clemens has received grants from NS Pharma during the conduct of the study as well as grants from Spark Therapeutics, Amicus Therapeutics, Sanofi Genzyme, ReveraGen BioPharma, NIH, MDA, and TRiNDS and personal fees from Epirium, outside the submitted work.
b. Dr Rao has received grants and personal fees from NS Pharma during the conduct of the study and nonfinancial support from Ann and Robert H. Lurie Children's Hospital of Chicago during the conduct of the study as well as personal fees from Biogen, Avexis/Novartis, Capricor, Regenxbio, Genentech-Roche, Scholar

Rock, PTC Therapeutics, Sarepta Therapeutics, France Foundation, and MDA outside the submitted work.

c. Dr Connolly has received grants from the Washington University School of Medicine and TRiNDS during the conduct of the study as well as grants from Sarepta Therapeutics, AveXis, and Fibrogen and personal fees from Sarepta Therapeutics, Scholar Rock, Genentech-Roche, Dyne Therapeutics, and Edgewise Therapeutics outside the submitted work.
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f. Dr McDonald has received grants from NS Pharma during the conduct of the study as well as personal fees from Avidity Biosciences, Astellas, Capricor Therapeutics, Catabasis Pharmaceuticals, Edgewise Therapeutics, Entrada Therapeutics, Epirium Bio, FibroGen, Italfarmaco, Pfizer, PTC Therapeutics, Roche, Santhera Pharmaceuticals, Solid Biosciences, and Sarepta Therapeutics outside the submitted work.
g. Dr Smith has received personal fees from NS Pharma during the conduct of the study as well as personal fees from Pfizer and Sarepta Therapeutics outside the submitted work.
h. Dr Zaidman has received grant support from Biogen and Novartis outside the submitted work.
i. Mr Nakagawa is an employee of NS Pharma, Inc.
j. Dr Hoffman has received fees from NS Pharma, holds stock and held oversight roles in AGADA Biosciences and TRiNDS during the conduct of the study, and holds stock and has management roles in ReveraGen BioPharma outside the submitted work.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JND-220811.

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EXHIBIT I

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Original Papers

Long-Term Safety and Efficacy Data of Golodirsen in Ambulatory Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping: A First-in-human, Multicenter, Two-Part, Open-Label, Phase 1/2 Trial

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The aim of this Phase 1/2, 2-part, multicenter trial was to report clinical safety and efficacy of long-term golodirsen treatment among ambulatory patients with exon 53 skip-amenable Duchenne muscular dystrophy (DMD). Part 1 was a 12-week, randomized, double-blind, placebo-controlled, dose-titration study followed by 9-week safety review. Part 2 was a 168-week, open-label evaluation of golodirsen 30 mg/kg. Part 1 primary endpoint was safety. Part 2 primary endpoints were dystrophin protein expression and 6-minute walk test (6MWT); secondary endpoints were percent predicted forced vital capacity (FVC%p) and safety. *Post hoc* ambulation analyses used mutation-matched external natural history controls. All patients from Part 1 (golodirsen, $n=8$; placebo, $n=4$) plus 13 additional patients entered Part 2; 23 completed the study. Adverse events were generally mild, nonserious, and unrelated to golodirsen, with no safety-related discontinuations or deaths. Golodirsen increased dystrophin protein (16.0-fold; $P<0.001$) and exon skipping (28.9-fold; $P<0.001$). At 3 years, 6MWT change from baseline was −99.0 m for golodirsen-treated patients versus −181.4 m for external controls ($P=0.067$), and loss of ambulation occurred in 9% versus 26% ($P=0.21$). FVC%p declined 8.4% over 3 years in golodirsen-treated patients, comparing favorably with literature-reported rates. This study provides evidence for golodirsen biologic activity and long-term safety in a declining DMD population and suggests functional benefit versus external controls. Clinical Trial Registration number: NCT02310906.

Keywords: golodirsen, Duchenne muscular dystrophy, exon skipping

Introduction

DUCHENNE MUSCULAR DYSTROPHY (DMD) is an X-linked, recessive, degenerative neuromuscular disease caused by mutations in the dystrophin (*DMD*) gene that disrupt the messenger RNA (mRNA) open reading frame, preventing translation of the dystrophin protein [1,2]. DMD is the most frequent hereditary muscle disease and affects 1 in every 3,500–5,000 boys born worldwide [3,4]. It is characterized by progressive muscle wasting and is universally fatal,

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with mean age of survival around the late 20s [5–7]. When treated with corticosteroids, patients <7 years of age typically improve their 6-minute walking test (6MWT) distance and may improve their North Star Ambulatory Assessment (NSAA) scores, but patients >7 years of age tend to exhibit progressive deterioration and declining ambulatory function, with loss of ambulation ~13 years of age [8–11].

Although progressive functional decline is common to all patients with DMD, natural history studies have revealed differences in the disease trajectories among patients according to steroid treatment, genetic modifiers, and, importantly, different underlying *DMD* mutations that have implications for their therapeutic management [1,8,12,13]. Mutations amenable to exon 53 skipping are present in ~8% of patients with DMD, and multiple independent studies have confirmed that these patients have more severe phenotypes compared with other patients with DMD, including earlier onset of decline, poorer muscle strength and function, and earlier loss of ambulation [1,8,14,15].

Exon-skipping therapies are designed to restore the *DMD* open reading frame and enable translation of internally shortened but functional dystrophin proteins [16,17]. Golodirsen [18] is one of four approved DMD-targeted exon-skipping therapies (the others being eteplirsen [19], viltolarsen [20], and casimersen [21]). Golodirsen is a phosphorodiamidate morpholino oligomer (PMO) designed for sequence-specific antisense binding to *DMD* pre-mRNA to induce skipping of exon 53. It was approved by the U.S. Food and Drug Administration in 2019 for the treatment of DMD in patients who have a confirmed mutation amenable to exon 53 skipping [18]. Approval was based on an observed increase in dystrophin protein expression after treatment.

This first-in-human study of golodirsen aimed to assess its long-term safety and biologic and clinical efficacy in a population of patients with DMD amenable to exon 53 skipping who were at an age associated with progressive deterioration and declining ambulatory function. Here, we report the results of the long-term, open-label part of the study, which evaluated golodirsen safety for up to 189 weeks and efficacy over 144 weeks.

Materials and Methods

Study design

This Phase 1/2, multicenter, 2-part study (NCT02310906) enrolled patients at four centers in France, Italy, and the United Kingdom [8]. Part 1 was a randomized, double-blind, placebo-controlled, dose-titration study to assess the safety, tolerability, and pharmacokinetics of four escalating doses of intravenous (IV) golodirsen over 12 weeks, followed by a 9-week safety review [22]. Part 2 was a long-term, 168-week, open-label evaluation of the biologic efficacy (at week 48), clinical efficacy (at week 144), and safety of golodirsen IV 30 mg/kg in patients with DMD amenable to exon 53 skipping. Clinical Trial Registration number is NCT02310906.

The Institutional Review Board or Independent Ethics Committee at each individual site reviewed and approved the protocol and consent forms. Written informed consent from each patient's parent(s) or legal guardian(s) and written assent from each patient were obtained. The study was designed and monitored in accordance with the ethical principles of the International Conference on Harmonisation Good Clinical Practice as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Patients

Eligible patients were male, 6–15 years old, with an established clinical diagnosis of DMD and a confirmed genetic mutation amenable to exon 53 skipping (except for untreated patients enrolled in Part 2, whose mutations were not amenable to exon 53 skipping). Participants were required to have stable cardiac and pulmonary function, and to be on a stable dose (or dose equivalent) of oral corticosteroids for ≥24 weeks before study initiation. Functional criteria included an ability to walk ≥250 m on the 6MWT at both screening and baseline and achieve a rise time <7 s (Gowers' s) or an NSAA total score >17.

Key exclusion criteria were the use of any pharmacologic treatment, aside from corticosteroids, that may have affected muscle strength or function within 12 weeks of study entry; current or previous treatment with experimental agents including BMN-195, PRO053, or other experimental treatments within 12 weeks; left ventricular ejection fraction <50% or corrected QT interval >450 ms; or percent predicted forced vital capacity (FVC%p) <50% at screening/baseline or need for nocturnal ventilation.

Treatment cohorts

In Part 1, patients were randomized 2:1 to receive either a weekly IV infusion of golodirsen or placebo at escalating dose levels, each for ≥2 weeks: 4 mg/kg in weeks 1 and 2, 10 mg/kg in weeks 3 and 4, 20 mg/kg in weeks 5 and 6, and 30 mg/kg beginning at week 7 (Fig. 1). In Part 2, treated patients from Part 1 and a further cohort of new patients with DMD amenable to exon 53 skipping received golodirsen 30 mg/kg/week for 168 weeks. In addition to these, a cohort of patients with mutations not amenable to exon 53 skipping was recruited to Part 2 of the study to evaluate exploratory biomarkers in patients with DMD with other genotypes (biomarker data to be reported elsewhere) and the natural history of the disease over 144 weeks. For treated patients who participated in Parts 1 and 2, the total study duration was 189 weeks.

Study endpoints and assessments

The primary objective of Part 1 was to evaluate the safety and tolerability of four escalating dose levels of golodirsen versus placebo. Safety assessments included adverse events (AEs), vital signs, physical examinations, clinical laboratory evaluations, electrocardiograms, and echocardiograms. Investigators assessed the severity of all AEs as mild, moderate, or severe, and determined whether AEs were related/unrelated to study treatment, procedures, and/or underlying disease.

AEs were considered treatment emergent (TEAEs) if they started, worsened, or became serious on or after the start of the first infusion and within 28 days after the last dose of study drug, or before receiving the first dose in the extension study. Serious AEs were defined as death, or events that were life threatening or resulted in inpatient hospitalization, persistent or significant disability/incapacity, or an important medical event. The secondary objective of Part 1 was pharmacokinetics (reported elsewhere [22]).

The primary biologic objective of Part 2 was to compare dystrophin expression in muscle biopsy samples at week 48

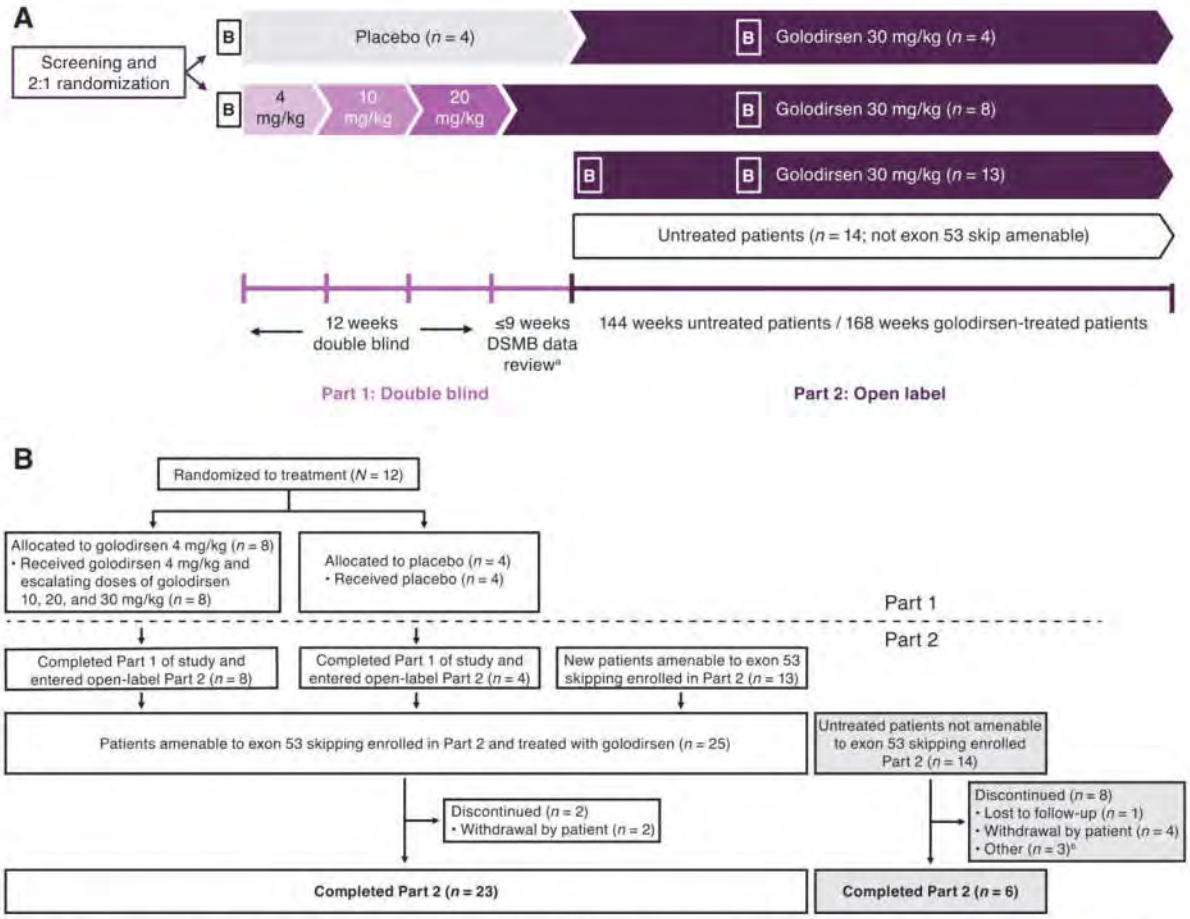

FIG. 1. **(A)** Study design. Part 1 was a double-blind, placebo-controlled, dose-titration period; each dose level was administered for ≥2 weeks. Part 2 was an open-label extension period, including all patients from Part 1 plus 13 new patients amenable to exon 53 skipping. The untreated arm consisted of patients not amenable to exon 53 skipping and, per protocol, was not a control group but was included to evaluate DMD natural history and exploratory biomarkers. Adapted with permission from Frank *et al.* [21]. DOI: https://doi.org/10.1212/WNL.0000000000009233. **(B)** Patient disposition. [a]Patients continued on treatment as randomized through enrollment and DSMB review. [b]Reasons included enrollment in a therapeutic study ($n = 2$) and personal reasons ($n = 1$). B, biopsy; DMD, Duchenne muscular dystrophy; DSMB, Data Safety Monitoring Board.

with baseline. The primary biologic endpoint was the change from baseline to week 48 in dystrophin protein levels as determined by western blot. The secondary biologic endpoints were change from baseline to week 48 in dystrophin intensity by immunohistochemistry, and exon 53 skipping determined using reverse transcription polymerase chain reaction. Biopsy samples were also examined *post hoc* for fetal/developmental myosin expression, a biomarker of myofiber regeneration that occurs after degeneration and is a prominent feature in DMD progression. Procedures for biologic analyses have been described previously [22–24].

The primary efficacy objective of Part 2 was to assess changes from baseline in ambulation in the treated patients; secondary efficacy objectives included assessment of respiratory function. The primary efficacy endpoint was change from baseline to week 144 on the 6MWT. Patients were considered to have lost ambulation if they received a score of 0 on both the NSAA walk and run components, or if the patient was unable to complete the NSAA test due to being nonambulatory at the time of the assessment. The secondary efficacy endpoint was change from baseline to week 144 in FVC%p. Safety was a secondary objective for Part 2.

Exploratory objectives (to be reported elsewhere) were to assess leg muscle morphology using magnetic resonance imaging, magnetic resonance spectroscopy, serum biomarkers, and extremity function and strength.

Post hoc *ambulation analysis*

To obtain data on golodirsen functional efficacy, comparisons were conducted with matched exon 53 skip-amenable natural history controls. External control patients were identified from a longitudinal multicenter cohort study in Italy, Belgium, and the United Kingdom [8], and matched to the golodirsen-treated group based on age (≥6 years), current steroid use, 6MWT distance (≥250 m), and ability

to rise from floor. Sufficiently matched longitudinal external control data were not available for pulmonary function; therefore, *post hoc* analyses were not possible for FVC%p.

Statistical analysis

Sample size for this study was based on qualitative considerations; no formal sample size calculations were performed. For Part 1, the safety set included all randomized patients who received ≥1 dose of study drug (golodirsen or placebo). For Part 2, the safety set included all randomized patients from Part 1, all Part 2 patients amenable to exon 53 skipping who received any amount of study drug, and all untreated patients who entered Part 2. The efficacy set comprised of all randomized patients from Part 1 and all Part 2 patients who had ≥1 postbaseline functional assessment.

AEs were analyzed using descriptive statistics. For all analyses, baseline was the last evaluation before golodirsen initiation. Changes in dystrophin expression were analyzed using a one-sample permutation *t*-test. In a *post hoc* analysis, correlation of exon skipping and dystrophin expression was analyzed using Spearman's correlation. *Post hoc* comparison of 6MWT with matched exon 53 skip-amenable natural history external controls was conducted using a two-sample *t*-test; loss of ambulation was compared with controls using Fisher's exact test. No formal comparisons were made for respiratory data. For all hypothesis testing, the two-sided significance level was 0.05 with no formal adjustment for multiplicity.

Results

Patients amenable to exon 53 skipping

A total of 12 patients were included in Part 1 (golodirsen, $n=8$; placebo, $n=4$). All patients completed Part 1 and continued into Part 2. An additional 13 patients entered the trial at the start of Part 2 (Fig. 1), resulting in a final cohort of 25 patients receiving open-label golodirsen 30 mg/kg/week in Part 2. Patients were 8.4 years of age on average (4 were <7 years of age), with average 35 months of corticosteroid use, an average 6MWT distance of 406 m, and an average FVC%p of 93% (Table 1). The mean duration of time on study during the combined study periods was 170.1 weeks, and patients received a mean of 164 infusions (median 167 infusions). Two patients withdrew before completion of Part 2 (patient decision at 73 and 98 weeks, respectively).

Safety

Safety was assessed in all golodirsen-treated patients ($n=25$), with exposure up to 189 weeks (mean 167 weeks).

TABLE 1. BASELINE CHARACTERISTICS OF GOLODIRSEN-TREATED PATIENTS AND MATCHED EXON 53 SKIP-AMENABLE NATURAL HISTORY CONTROLS

Baseline characteristic[a]	*Golodirsen-treated patients* (n=25)	*Matched exon 53 skip-amenable natural history controls* (n=19)	P
Age, years	8.4 (2.2)	9.1 (1.7)	0.17
Range	6–13	6–11.6	
Height, cm	120.5 (10.1)	N/A	
Weight, kg	28.4 (9.0)	N/A	
BMI, kg/m^2	19.1 (3.7)	N/A	
Mutation, *n* (%)			
45–52	8 (32.0)	2 (10.5)	
48–52	5 (20.0)	9 (47.4)	
49–52	5 (20.0)	3 (15.8)	
50–52	4 (16.0)	1 (5.3)	
52	3 (12.0)	4 (21.1)	
6MWT distance, m	405.8 (55.1)	382.1 (55.9)	0.17
Range	290–512	300–489	
Time to rise from floor, s	5.9 (3.5)	6.2 (3.1)	0.76
Range	2.3–18.6	3–14.9	
NSAA	23.6 (5.0)	N/A	
Range	13–33	N/A	
FVC%p	92.7 (24.0)	N/A	
Range	16.4–137.8	N/A	
Time since DMD diagnosis, months	55.8 (24.8)	N/A	
Range	16.1–122.9		
Duration of corticosteroid use, months	35.3 (24.4)	N/A	
Range	8.9–97.7		
Frequency of corticosteroid administration, *n* (%)			
Continuous	19 (76.0)	7 (36.8)	
Intermittent	6 (24.0)	12 (63.2)	
Corticosteroid type, *n* (%)			
Deflazacort	12 (48.0)	N/A	
Prednisone	13 (52.0)	N/A	

Values are mean (SD) unless noted otherwise.
[a]For golodirsen-treated patients, baseline was defined as the last assessment before golodirsen initiation.
6MWT, 6-minute walk test; BMI, body mass index; DMD, Duchenne muscular dystrophy; FVC%p, percent predicted forced vital capacity; N/A, not available; NSAA, North Star Ambulatory Assessment; SD, standard deviation.

TABLE 2. ADVERSE EVENTS OVERVIEW

AEs, n (%)	Part 1		Combined Parts 1 and 2
	Placebo (n=4)	Golodirsen (n=8)	Total golodirsen (n=25)
Patients with ≥1 AE, *n* (%)	4 (100)	8 (100)	25 (100)
Related to study drug	2 (50.0)	5 (62.5)	9 (36.0)
Serious	0	0	4 (16.0)
Leading to study drug discontinuation	0	0	0
Total AEs by severity, *n*	23	69	860
Mild	22	68	831
Moderate	1	1	24
Severe	0	0	5

AE, adverse event.

In both the double-blind period (Part 1) and the open-label period (Part 2), all patients experienced ≥1 AE (Table 2). Most AEs were mild, nonserious, and assessed by the investigator as unrelated to golodirsen. Five AEs were deemed severe (all were events of fracture or inability to walk), but none were considered serious.

No anaphylaxis or serious hypersensitivity events were reported. Infusions were well tolerated, and the majority of infusion-related reactions were mild and nonserious; none were severe. Of infusion-related reactions, five were possibly related to golodirsen, including pyrexia, rash, tachycardia, erythema, and decreased blood pressure (all mild). There was no evidence of serious kidney toxicity. Two patients experienced mild renal AEs (both proteinuria) that were transient and nonserious, and resolved spontaneously. No patient discontinued treatment because of AEs. There were no deaths in the study.

In total, nine patients experienced treatment-related TEAEs (Table 3). Treatment-related pyrexia, headache, and proteinuria each occurred in >1 patient. Cardiac events possibly related to golodirsen were reported in two patients [tachycardia ($n=1$; 30 minutes after infusion) and syncope ($n=1$; 5 days after infusion)]; both were nonserious and mild, and both resolved without intervention and did not lead to treatment discontinuation. Syncope did not recur during the study. Two further instances of heart rate >125 bpm occurred 60 min post infusion in the patient with tachycardia. Four (15%) patients experienced seven serious AEs (vomiting, pyrexia, hypocalcemia, hematemesis, viral gastroenteritis, convulsion, and tonsillar hypertrophy); all were deemed to be unrelated to golodirsen treatment.

TABLE 3. STUDY DRUG-RELATED TREATMENT-EMERGENT ADVERSE EVENTS IN COMBINED PARTS 1 AND 2

AEs, n (%)	Total golodirsen group (n=25)
Any TEAE related to study drug	9 (36.0)
Pyrexia	3 (12.0)
Headache	2 (8.0)
Proteinuria	2 (8.0)
Syncope	1 (4.0)
Erythema	1 (4.0)
Rash	1 (4.0)
Skin exfoliation	1 (4.0)
Sinus tachycardia	1 (4.0)
Tachycardia	1 (4.0)
Gastroenteritis	1 (4.0)
Blood pressure decreased	1 (4.0)
Hyperglycemia	1 (4.0)

TEAE, treatment-emergent adverse event.

To deliver golodirsen, a port-a-cath was inserted in six patients before starting study drug, and in one patient after the first three doses of golodirsen. The total number of infusions given through port was 1,185, accounting for 94% of expected doses in those patients (6% of doses missed). Median age of patients receiving a port was 10.7 years. AEs related to the port were reported in five patients, and included catheter site bruising ($n=3$), catheter site pain ($n=3$), catheter site rash ($n=1$), peripheral swelling ($n=1$), and infection related to the port ($n=1$). None of the patients who received a port withdrew from the study.

Exon skipping and dystrophin expression

We have previously reported that at week 48, exon skipping and dystrophin expression were both significantly increased (all $P<0.001$) among patients treated with golodirsen, and positive correlation was observed between exon 53 skipping and dystrophin production (Spearman's correlation coefficient: 0.50; $P<0.02$) [22]. Treatment with golodirsen (Parts 1 and 2 combined) resulted in a significant, 16.0-fold mean increase in dystrophin protein levels detected by western blot, from a baseline mean of 0.095% of normal levels, to 1.019% of normal at week 48 ($P<0.001$; Fig. 2A).

Similarly, the level of exon 53-skipped *DMD* gene expression was found to be increased by 28.9-fold ($P<0.001$; Fig. 2B). We also reported that the percentage of dystrophin-positive fibers was significantly increased at week 48 (13.5-fold increase; $P<0.001$; Fig. 2C) [22], and that myofiber regeneration decreased after golodirsen treatment, indicated by fewer fibers positive for fetal/developmental myosin at week 48 compared with baseline (Fig. 2D) [23].

Ambulatory and pulmonary function

Mean 6MWT distance at baseline was 405.8 m for golodirsen-treated patients and declined by 26.1, 64.6, and 99.0 m at weeks 48, 96, and 144, respectively (Table 4). Two of 25 patients lost ambulation. Among golodirsen-treated patients, FVC%p declined by 8.4% over 3 years of treatment, from a mean FVC%p of 92.7% at baseline to 83.8% at week 144.

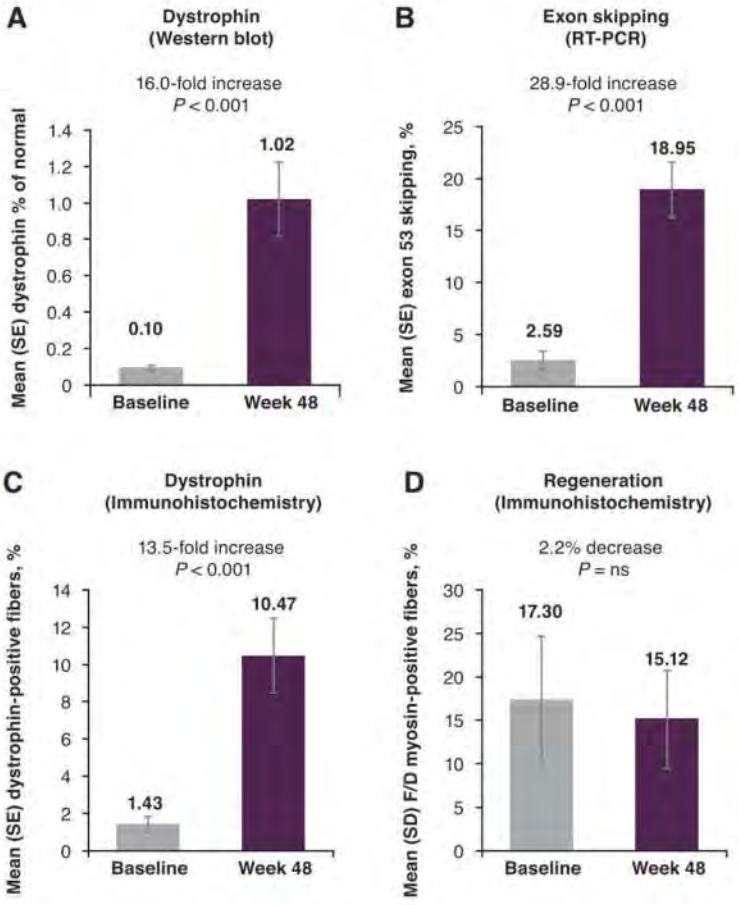

FIG. 2. **(A)** Mean dystrophin protein by western blot, **(B)** exon skipping by RT-PCR, **(C)** dystrophin protein by immunohistochemistry, and **(D)** percentage of F/D myosin-positive fibers were measured at baseline and after 48 weeks of golodirsen treatment. F/D, fetal/developmental; ns, not significant; RT-PCR, reverse transcription polymerase chain reaction.

Post hoc *ambulation analysis*

From the external control natural history cohort [8], 28 patients were identified who were amenable to exon 53 skipping and had longitudinal 6MWT assessments for comparison. Of these, 19 patients were successfully matched according to the golodirsen-treated group inclusion criteria; 9 patients did not meet matching criteria and were excluded (age <6 years, $n=6$; steroid naive, $n=1$; unable to rise, $n=2$). Patients treated with golodirsen had a numerically longer mean baseline 6MWT distance compared with the matched controls, but this was nonsignificant ($P=0.17$); otherwise, available baseline characteristics were similar between these two groups (Table 1).

Control patients' 6MWT distance declined by a mean of 181.4 m [standard deviation (SD), 151.6; range, −401 to 56] after 3 years compared with baseline. In contrast, golodirsen-treated patients maintained a more stable trajectory, with a mean decline from baseline of 99.0 m (SD, 123.8; range, −368 to 144) after 3 years ($P=0.067$ between groups; Fig. 3A).

TABLE 4. AMBULATORY AND PULMONARY FUNCTION IN GOLODIRSEN-TREATED PATIENTS

Endpoints	*Baseline*[a]	*Week 48*	*Week 96*	*Week 144*
6MWT, m	$n=25$	$n=23$	$n=24$	$n=22$
Mean (SD)	405.8 (55.1)	378.9 (93.2)	344.1 (128.9)	311.0 (143.4)
Range	290–512	81–541	0–523	0–481
Mean (SD) change from baseline		−26.1 (65.1)	−64.6 (105.1)	−99.0 (123.8)
Loss of ambulation	$n=25$	$n=25$	$n=24$	$n=23$
n (%)	0	0	1 (4.0)	2 (9.0)
FVC%p	$n=25$	$n=24$	$n=23$	$n=23$
Mean (SD)	92.7 (24.0)	92.5 (18.7)	93.9 (17.6)	83.8 (23.2)
Range	16.4–137.8	41.9–129.9	37.4–124.9	7.8–121.1
Mean (SD) change from baseline		−0.63 (21.5)	0.79 (23.8)	−8.38 (29.5)

[a]Baseline FVC%p for placebo patients was defined as Part 2 baseline FVC%p, and inclusion criteria (FVC%p > 50%) for screening were not applied at that time.

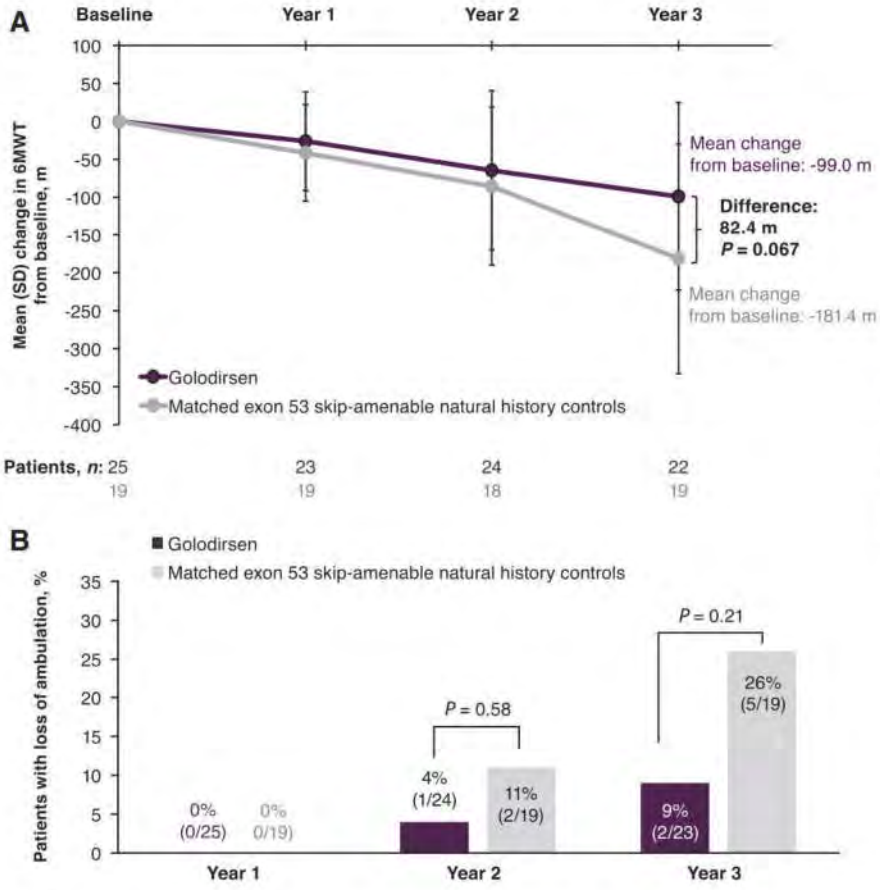

FIG. 3. Ambulatory function: **(A)** 6MWT distance and **(B)** loss of ambulation over 3 years in golodirsen-treated patients and matched exon 53 skip-amenable natural history external controls. 6MWT, 6-minute walk test.

This difference emerged over time, as no difference between treated and untreated patients was observed at the time points before year 3. Among natural history controls, 5 of 19 patients (26%) had lost ambulation over 3 years, compared with 2 of 25 (9%) of those who received golodirsen ($P = 0.21$; Fig. 3B).

Untreated arm (not amenable to exon 53 skipping)

Genotypes of patients in the untreated arm are presented in Table 5, and included genotypes associated with a milder clinical course, such as mutations amenable to exon 44 skipping. The untreated arm was intended to evaluate the natural history of disease and, specifically, exploratory biomarkers that are still under investigation. Per protocol, it was not considered a control group for efficacy comparison of golodirsen-treated patients, given the differences in disease trajectories demonstrated for patients with differing DMD genotypes [1,8,12,13].

The untreated arm in Part 2 included 14 patients. Eight patients discontinued before the end of the follow-up period (one was lost to follow-up, four withdrew, two enrolled in a therapeutic study, and one discontinued for personal reasons). Mean (SD) age was 8.5 (1.9) years (range, 6–12 years). Outcomes for the untreated patients are shown in Table 5. Declines in both ambulatory and pulmonary functions were observed from baseline to week 144.

TABLE 5. UNTREATED ARM FUNCTIONAL OUTCOMES

Endpoints	*Baseline*	*Week 144*
6MWT distance	$n = 13$	$n = 6$
Mean (SD)	455.1 (51.1)	278.7 (188.9)
Range	351–539	0–525
FVC%p	$n = 13$	$n = 5$
Mean (SD)	97.9 (18.3)	77.5 (18.6)
Range	60.85–120.51	53.86–99.96

Genotypes in the untreated arm included ($n = 1$ each) 1–47, 3–7, 7–17, 8–43, 10–21, 22–25, 30–43, 35–43, 45, 45–50, 46–51, 46–52, 51, and 61–62.

Discussion

The results presented herein provide evidence for the biologic activity and long-term safety of golodirsen in a declining DMD population, supporting evaluation of golodirsen in an ongoing Phase 3 trial (NCT02500381). Although the study was not powered or designed to demonstrate efficacy, *post hoc* analysis using an external control suggests possible functional benefit after a 3-year exposure.

The data show that long-term treatment with golodirsen, assessed at a dose of 30 mg/kg/week, is well tolerated in patients with DMD amenable to exon 53 skipping. During long-term treatment, AEs were generally mild, nonserious,

and unrelated to golodirsen, and there were no discontinuations due to safety. Most AEs were consistent with conditions that may be anticipated in the pediatric population, and with complications or comorbidities of the underlying DMD.

There was no suggestion of a serious risk of kidney abnormality or toxicity. Mild cardiac events possibly related to golodirsen were reported in two patients (tachycardia in an 8-year-old patient on day 8 and syncope in a 13-year-old patient on day 13), but both were nonserious, resolved, and did not lead to treatment discontinuation. These cardiac events may have been confounded by underlying disease. No anaphylaxis or serious hypersensitivity was observed.

The safety profile of golodirsen is consistent with that of other approved PMOs targeting different exons, such as eteplirsen and casimersen [19,21,22,25–27]. Both of these have been previously shown to increase dystrophin production, with a tolerability profile revealing neither renal nor hepatic safety signals, and serum chemistry and properties within expectations given the progression of DMD.

Seven of 25 patients in this study received a venous port for administration of golodirsen to ease the burden of weekly IV infusions. In these patients, use of the port to receive golodirsen was successful, but did not affect the level of treatment compliance (94% in patients with a port vs. 95% in patients without). AEs related to the port were generally limited to pain and bruising; infection related to the port was observed in only one patient (out of seven who had a port). All patients who received ports completed the study, and no withdrawals were due to port-related AEs. The successful use of ports eases the administration burden for golodirsen and the distress for patients associated with weekly cannulation.

The potential functional benefits of golodirsen emerged with detection of increased exon skipping and dystrophin protein in golodirsen-treated patients, and these two measures of biologic activity were positively correlated. Over 48 weeks, exon skipping increased 28.9-fold, dystrophin protein increased 16.0-fold, reaching ~1%, and percentage of dystrophin-positive fibers increased 13.5-fold compared with baseline [22].

These complementary bioanalytical techniques were used to confirm that the relative increase in dystrophin production was correlated with correct localization and distribution of the protein at the sarcolemma of the muscle fibers. Animal studies [28] and clinical studies [29,30] have shown that even low levels of dystrophin can improve functional outcomes in DMD and are associated with milder dystrophinopathy. In one recent study, achieving dystrophin quantities <0.5% of normal was associated with a milder clinical phenotype and a delay to loss of ambulation, suggesting that any increase in dystrophin protein is beneficial [30]. Further, studies of other PMOs show that dystrophin accumulates with long-term treatment, including at time points beyond 48 weeks [26,31,32].

In vitro studies have also demonstrated the molecular functionality of dystrophin protein produced by DMD myotubes after golodirsen treatment [24]. Consistently, we have previously demonstrated in post-treatment biopsy data from golodirsen-treated patients that increased dystrophin was associated with a 2.2% decrease in fibers positive for the regeneration marker fetal/developmental myosin [23].

Although this change did not reach statistical significance, a previous trial on an unsuccessful DMD treatment showed a 1.2% increase [confidence interval (95% CI) −1.1 to 3.4] in myofibers positive for fetal/developmental myosin over 48 weeks [33]. Together, these results suggest a histologic benefit with golodirsen treatment and provide evidence of protection from the ongoing muscle dystrophic process. In aggregate, the biologic data from our study demonstrate target engagement by golodirsen, and achievement of dystrophin levels and histologic benefits that are likely to predict clinical benefit.

Comparative efficacy assessments in DMD therapy trials are complicated by the small numbers of patients with matched genetic mutations and the unsuitability of patients with nonmatched mutations as controls. This is particularly relevant for early (Phase 1/2) studies, in which a placebo arm is usually not planned for longer term observation. Although longer term placebo-controlled studies are desirable to increase the level of evidence, there is limited participant willingness to be exposed only to placebo during a time of irreversible function loss [34]. For exon-skipping therapies, maximal therapeutic effects may not be apparent in short-term studies [35]. Studies of other exon-skipping therapies have also met with these challenges in study design, and have used mutation-matched external controls to compare efficacy assessments [36,37].

Therefore, an external natural history cohort, matched for mutation class and baseline functional capability, offered the most relevant comparator group to assess golodirsen efficacy [8]. Compared with these matched exon 53 skip-amenable natural history controls, golodirsen treatment possibly attenuated ambulatory function loss, slowing decline and helping treated patients maintain a more stable trajectory. Similarly, a smaller proportion of golodirsen patients lost ambulation over the 3-year study period than natural history patients (9% vs. 26%).

Although statistical significance could not be reached with these small sample sizes, this unpowered study suggests that golodirsen treatment elicits a promising departure from natural history. The gradual divergence of the evolution in comparison with untreated patients is consistent with the mode of action and the accumulation of dystrophin with continued treatment.

Patients selected for the study were in an age range (6 – 15 years) in which the DMD natural history is in a phase of progressive deterioration, including declining ambulatory function leading to loss of ambulation [8–11]. The study also included four patients <7 years of age; patients at the younger end of the age range may have shown functional improvement due to the effect of physiologic growth and development, confounding assessment of treatment effect. Nevertheless, these patients followed a trajectory consistent with the overall study population.

Numerous publications have documented rates of FVC%p decline in mixed-genotype cohorts, with an average annual rate of loss between 4.5% and 7% [12,38–47], including patients taking corticosteroids [48]. Values vary depending on the patient cohort studied, with age impacting the rate of pulmonary function loss [44,45]. Corticosteroid use may further affect pulmonary function by delaying the onset of decline [12,48]. When analyzed by genotype, pulmonary function was worse in patients amenable to exon 53 skipping compared with other mutations [12]. In our study, exon 53 skip-amenable patients receiving golodirsen showed 8.4% FVC%p loss over 3 years.

A previous study performed in an Italian and U.S. cohort of patients with DMD ($N=37$) assessed the influence of genotypes on respiratory function, and concluded that exon 53 skip-amenable patients had the worst outcomes [12]. These patients had an annual FVC%p decline of 4.9% between the ages of 8.7 and 22.6 years, and also began with lower FVC%p at age 8.7 years compared with patients with other mutations [12] (L. Bello and E. Pegoraro, personal communication). Some of the patients in this previous study were taking corticosteroids, which have been shown to improve respiratory function, regardless of whether the steroid regimen was daily or intermittent [48].

Our study was designed to assess the safety and proof of mechanism of golodirsen, with no control group planned *a priori* for efficacy. Other limitations included the small sample size and the *post hoc* nature of the efficacy comparisons to external controls. In addition, patients in our study were evaluated for ambulation, a measure on which they were already declining at baseline. The effect of golodirsen on functions that were intact at the time of treatment initiation, such as upper limb function, needs to be explored.

Finally, our analysis of exon skipping was performed using reverse transcription PCR rather than more quantitative methods such as quantitative PCR or droplet digital PCR [49]. This method was chosen in consultation with the U.S. FDA during protocol development to demonstrate exon skipping and has been previously used to characterize exon skipping for other approved therapies [26,50].

Further quantitative analysis of golodirsen's exon-skipping properties will be an area for future research. Importantly, however, dystrophin protein expression as measured by western blot and immunofluorescence (percent dystrophin-positive fibers) was demonstrated utilizing a validated and quantitative methodology, confirming the ability of golodirsen to induce exon skipping and dystrophin protein production.

The results from this study provide evidence for the biologic activity and long-term safety of golodirsen 30 mg/kg/week in a declining population of patients with DMD and confirmed mutations amenable to exon 53 skipping. *Post hoc* comparisons of ambulation outcomes with external controls suggest functional benefit that can be measured after a 2-year period. Similarly, the cumulative 3-year decline in FVC%p among golodirsen-treated patients is compared favorably with literature-reported estimates of annual natural history decline. Overall, the data hold promise for functional benefits of golodirsen, warranting larger studies. A Phase 3, placebo-controlled, double-blind study (NCT02500381) is underway.

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Author Disclosure Statement

L.S. has served on advisory boards for Sarepta Therapeutics, Inc.; E.M. has received consultant fees from Sarepta Therapeutics, Inc.; V.S. has received speaker honoraria from Sanofi Genzyme, is or has recently been on advisory boards for Audentes Therapeutics, Biogen, Exonics Therapeutics/Vertex, Novartis, Roche, Sarepta Therapeutics, Inc., and Wave Therapeutics, and has research collaborations with Sanofi Genzyme and Ultragenyx; M.G. has received speaker honoraria from Sarepta Therapeutics, Inc., is on advisory boards for Pfizer, has research collaboration with Sarepta Therapeutics, Inc., and is the Chair of the VBP15-004 study but does not have any financial interest with ReveraGen; A.M.S., M.S., and D.L. have nothing to disclose; E.K., N.K., A.D., X.W., B.H., and D.W. are or have been employees of Sarepta Therapeutics, Inc.; F.M. has received consultant fees and speaker honoraria from Sarepta Therapeutics, Inc., and is supported by the NIHR Great Ormond Street Hospital Biomedical Research Centre.

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Research Report

Efficacy and Safety of Viltolarsen in Boys With Duchenne Muscular Dystrophy: Results From the Phase 2, Open-Label, 4-Year Extension Study

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Abstract.
Background: Duchenne muscular dystrophy (DMD) is caused by DMD gene mutations, resulting in absence of functional dystrophin protein. Viltolarsen, an exon 53 skipping therapy, significantly increased dystrophin levels in patients with DMD. Presented here are completed study results of >4 years of functional outcomes in viltolarsen-treated patients compared to a historical control group (Cooperative International Neuromuscular Research Group Duchenne Natural History Study [CINRG DNHS]).
Objective: To evaluate the efficacy and safety of viltolarsen for an additional 192 weeks in boys with DMD.

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Methods: This phase 2, open-label, 192-week long-term extension (LTE) study (NCT03167255) evaluated the efficacy and safety of viltolarsen in participants aged 4 to < 10 years at baseline with DMD amenable to exon 53 skipping. All 16 participants from the initial 24-week study enrolled into this LTE. Timed function tests were compared to the CINRG DNHS group. All participants received glucocorticoid treatment. The primary efficacy outcome was time to stand from supine (TTSTAND). Secondary efficacy outcomes included additional timed function tests. Safety was continuously assessed.
Results: For the primary efficacy outcome (TTSTAND), viltolarsen-treated patients showed stabilization of motor function over the first two years and significant slowing of disease progression over the following two years compared with the CINRG DNHS control group which declined. Viltolarsen was well tolerated, with most reported treatment-emergent adverse events being mild or moderate. No participants discontinued drug during the study.
Conclusions: Based on the results of this 4-year LTE, viltolarsen can be an important treatment strategy for DMD patients amenable to exon 53 skipping.

Keywords: Duchenne muscular dystrophy, dystrophin, viltolarsen, exon skipping, clinical efficacy

INTRODUCTION

Duchenne muscular dystrophy (DMD) is an X-linked, recessive, neuromuscular disorder resulting from DMD gene mutations (deletions, duplications, nonsense mutations) causing a loss of dystrophin protein and function in striated muscle [1, 2]. DMD occurs in approximately 1 : 3600 to 1 : 9300 male births [1]. Patients with DMD experience degeneration of skeletal muscle and resultant muscle weakness, resulting in respiratory failure and cardiac insufficiency leading to premature death [3–5]. However, new therapeutic advances for DMD have emerged that include exon skipping and gene therapy, with a goal to slow disease progression [5–8]. More specifically, exon skipping therapies designed for the treatment of DMD are capable of providing expression of truncated dystrophin protein in skeletal muscle and, in return, may delay the progression of the disease [9, 10].

Exon skipping therapies use antisense oligonucleotides to restore the open reading frame of the pre-messenger RNA by changing DMD out-of-frame deletions to in-frame deletions [11, 12]. Approximately 8% to 10% of patients with DMD have DMD gene deletions that are amenable to exon 53 skipping, a treatment approach that can restore the reading frame and promote production of an internally shortened dystrophin protein, which has the capability to provide partial function [2, 11, 12]. Viltolarsen is an antisense oligonucleotide designed to treat DMD in patients with a confirmed mutation of the DMD gene amenable to exon 53 skipping [13]. Viltolarsen is approved in the US by the Food and Drug Administration (FDA) and in Japan for the treatment of DMD based on a significant increase in muscle dystrophin expression that was evident in clinical trials [10, 13–15].

An initial phase 2, randomized, 24-week clinical trial that evaluated the efficacy, safety, and tolerability of viltolarsen in boys 4 to < 10 years of age with DMD demonstrated muscle dystrophin production [13]. All 16 participants showed an increase in dystrophin levels, measured by a validated western blot assay at the end of the 24 weeks of treatment [13]. Further, a mean dystrophin value of 5.9% was achieved at the recommended 80 mg/kg/week dosage [13]. The western blot data were supported by significant increases in dystrophin mRNA splicing on reverse transcription–polymerase chain reaction, dystrophin protein by mass spectrometry, and percentage of dystrophin-positive myofibers by immunohistochemistry [13]. Participants treated with viltolarsen showed improvements in timed function tests from baseline for time to stand from supine (TTSTAND) and time to run/walk 10 meters (TTRW) compared with a group-matched historical control group (Cooperative International Neuromuscular Research Group Duchenne Natural History Study [CINRG DNHS]) [13]. Overall, viltolarsen was well tolerated, with no reports of treatment-related serious adverse events (SAEs), discontinuations, or deaths occurring in the study [13]. At the conclusion of the 24-week study, all participants were given the opportunity to enroll in the long-term extension (LTE) study (NCT03167255) [13].

The primary objective of the LTE study was to evaluate the effects on mobility and safety of 40- or 80-mg/kg/week intravenous doses of viltolarsen for an additional 192-week treatment period for a total of 216 weeks of treatment from the start of the initial phase 2 study to the completion of the open-label extension study. An interim analysis at 2 years was published, and the data presented here are the final results following 4 years of treatment [10].

MATERIALS AND METHODS

Participants and trial design

All participants ($N = 16$) of the initial 24-week, phase 2 study (NCT02740972) continued into the phase 2, open-label, LTE study to assess long-term efficacy, assessed by timed muscle function tests, and safety of viltolarsen for up to an additional 192 weeks (NCT03167255; Fig. 1). Participant enrollment occurred at six sites across the US and Canada. Participants (4 to < 10 years of age when enrolled in the initial phase 2 study) continued to receive weekly viltolarsen at the dosage received in the initial 24-week study. Participants enrolled in the LTE study received treatment for the duration of the study (up to 216 weeks of total treatment, including initial study, plus a 30-day posttreatment phase). Viltolarsen was administered as an intravenous infusion over one hour at a dosage of 40 or 80 mg/kg once weekly. Following the Institutional Review Board approval (and per advisement from the US FDA), all participants who were receiving 40 mg/kg/week since the start of the initial study were dose increased to 80 mg/kg/week for the remainder of their participation in the LTE study. The first participant in the low-dose cohort was switched at week 178 and the remaining seven participants were switched by week 197. Participants were required to remain on a stable dose of glucocorticoid for the duration of the study. Although no participants were excluded, exclusion criteria included all those who experienced SAEs or severe AEs in the initial study that were related to the study drug, and those who received treatment for dystrophin or dystrophin-related protein indication or other new investigational drugs after completion of the initial 24-week study. Populations representing gene deletions amenable to exon skipping of exon 44 or deletions of exons 1–8 were not represented as a comparator in the historical control group because these mutation groups typically have a milder disease progression. The clinical study protocol was approved by the Institutional Review Board and this study was performed according to the Good Clinical Practice and International Conference on Harmonization regulations, the code of federal regulations, US FDA, and principles of the Declaration of Helsinki.

Outcomes and assessments

Efficacy assessments were performed every 12 weeks. Efficacy was measured by timed function tests, including TTSTAND (primary endpoint), secondary endpoints of TTRW, time to climb 4 stairs (TTCLIMB), North Star Ambulatory Assessment (NSAA), and six-minute walk test (6MWT). The timed results for TTSTAND, TTCLIMB, and TTRW were converted to velocities, and both time and velocity results are presented. The rationale for converting to velocity is to provide a way to include participants who were no longer able to perform the tests mentioned in the analysis for that visit. Efficacy assessments were compared to historical controls (CINRG DNHS), who were group matched for geographic location, age, glucocorticoid use, and ambulatory ability at baseline, defined as all participants being able to execute TTSTAND, TTRW, and TTCLIMB, at baseline. The last time point in which efficacy assessments were available for both the viltolarsen and CINRG DNHS groups was week 205 due to the schedule of CINRG DNHS assessments; therefore, week 205 is the last assessment date in the analysis set. Safety was assessed at each visit or participant contact throughout the duration of the

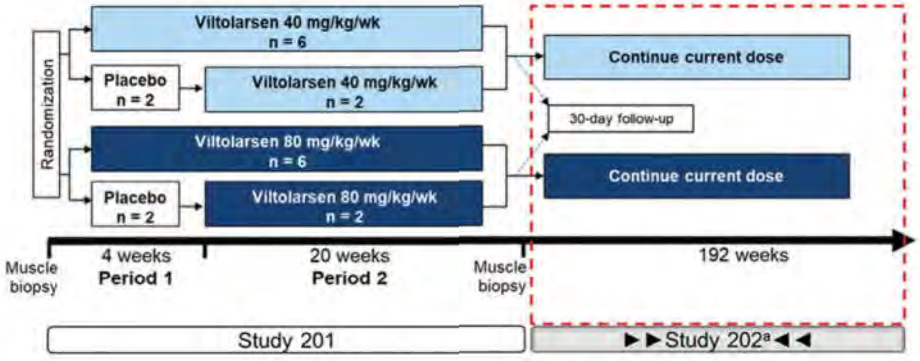

Fig. 1. Study design. [a]The first participant who received 40 mg/kg/week was increased to the higher dose (80 mg/kg/week) at wk 178 with the remaining participants switching to the higher dose by wk 197. Wk, week.

study. Treatment-emergent adverse events (TEAEs) and SAEs were assessed during the safety analysis. Before performing any study-related activities, parents or legal guardians of the participants provided written informed consent and Health Insurance Portability and Accountability Act authorization.

Statistical analysis

The sample size in this study was determined from the participants who completed the initial 24-week study and enrolled into the LTE study. Therefore, the sample size was not based on any statistical considerations. Statistical considerations and power to detect statistical differences were aligned with the initial 24-week study [13].

All timed function tests were performed using the full analysis set (FAS), which included all participants who received ≥ 1 dose of viltolarsen in both the initial 24-week study and LTE study. The safety population, which was the primary analysis population for safety assessments, was identical to the FAS. Efficacy outcome measures were tested between study participants and the CINRG DNHS control group using a mixed-effects linear model. All statistical tests were two-sided and performed at a significance level of 0.05 using SAS v9.4 or higher.

RESULTS

Participants

All participants (N = 16) who completed the initial 24-week, phase 2 study qualified and transitioned into the LTE study. The majority of participants were White (15/16, 94%), with mean age in the LTE study being 7.9 years. Two participants enrolled when they were 4 years old. Overall, baseline characteristics between participants in the two dosage cohorts were balanced and similar to the CINRG DNHS controls (Table 1). All participants in the study and the CINRG DNHS external control set received chronic treatment with glucocorticoids.

Efficacy outcomes

Timed function tests were used to indicate DMD progression. For the primary efficacy endpoint (TTSTAND) participants who received viltolarsen showed stabilization of motor function over the first two years and a significant slowing of motor function loss over the following two years, whereas a more significant decline was observed in the CINRG DNHS comparator group over the entire 4-year period (Fig. 2). Change from baseline improvements were statistically significant ($P < 0.05$) for TTSTAND (seconds) beginning at week 73 and remained significantly different through week 205 (Fig. 2A), and for TTSTAND (velocity) beginning at week 37 and remained significantly ($P < 0.05$) different through week 205 (Fig. 2B).

Similarly, the change from baseline for TTRW showed stabilization of motor function over the first two years and significant slowing of motor function loss over the following two years for viltolarsen-treated participants compared with the CINRG DNHS comparator group (Fig. 3A). The change from baseline (seconds) was significant for TTRW at the beginning of week 73 ($P = 0.01$) and remained significantly different through week 205 ($P \leq 0.0001$) and for TTRW (velocity) beginning at week 37 ($P = 0.01$) and remained significantly different through week 205 ($P \leq 0.0001$). TTCLIMB (seconds) did not show a significant difference between the viltolarsen and the CINRG DNHS comparator group, whereas TTCLIMB (velocity) was significant at week 73 ($P = 0.01$) and week 205 ($P = 0.007$) (Fig. 3B). 6MWT and NSAA efficacy endpoints were added later in the clinical study to the CINRG DNHS protocol, and as a result the historical comparator control group did not have sufficient data on 6MWT and NSAA to adequately compare with

Table 1
Participant baseline demographics

Characteristics	Viltolarsen cohort, mean			CINRG DNHS control cohort, mean		
	40 mg/kg/wk ($n = 8$)	80 mg/kg/wk ($n = 8$)	Total ($N = 16$)	Exon 53 amenable controls ($n = 9$)	Non-exon 53 amenable controls ($n = 56$)	Total ($N = 65$)
Age, years	7.5	7.2	7.4	6.3	7.2	7.1
Weight, kg	23.7	22.3	23.0	21.6	24.4	24.0
Height, cm	114.6	112.2	113.4	111.3	116.6	115.8
BMI, kg/m^2	17.9	17.4	17.6	17.3	17.5	17.5

BMI, body mass index; CINRG, Cooperative International Neuromuscular Research Group; DNHS, Duchenne Natural History Study.

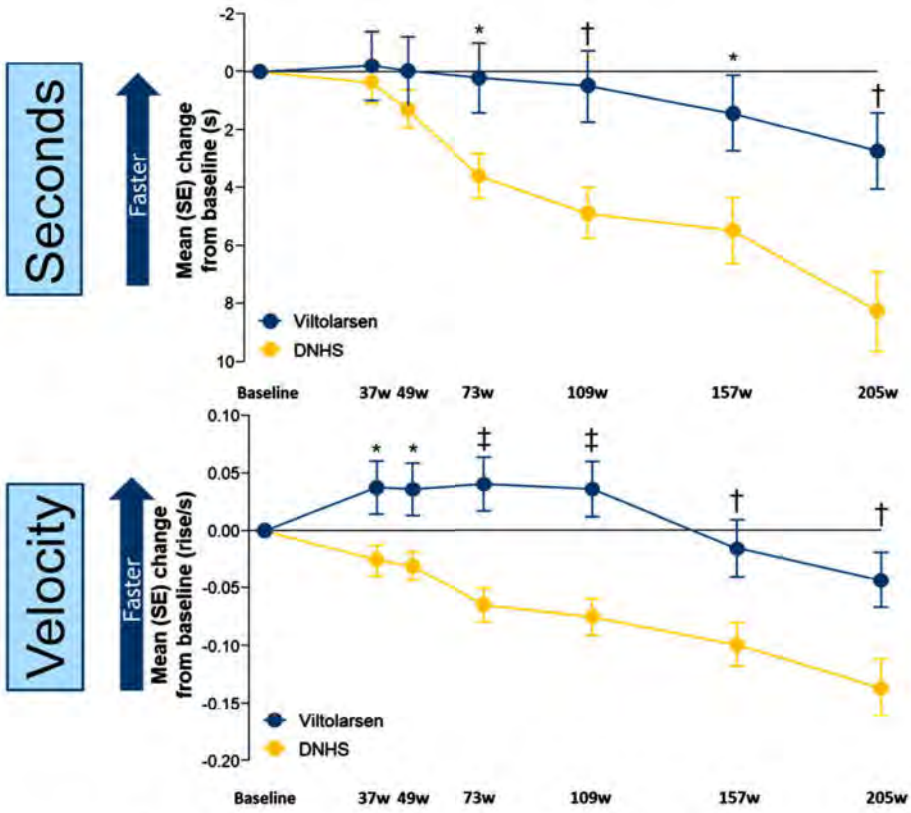

Fig. 2. Timed Function Tests: Change From Baseline vs Natural History Controls for TTSTAND. *$P<0.05$; †$P<0.01$; ‡$P \leq 0.001$. DNHS, Duchenne Natural History Study; s, seconds; SE, standard error; TTSTAND, time to stand from supine; w, weeks. TTSTAND (seconds) Viltolarsen sample size (n): 16, 16, 15, 14, 14, 11, 13. TTSTAND (seconds) CINRG DNHS sample size (n): 65, 31, 57, 24, 24, 14, 10. TTSTAND (velocity) Viltolarsen sample size (n): 16, 16, 15, 14, 14, 11, 14. TTSTAND (velocity) CINRG DNHS sample size (n): 65, 31, 58, 28, 28, 20, 12.

the viltolarsen-treated participants [10]. The 6MWT distances over the 4-year period for the viltolarsen-treated group similarly showed stable measures, as did NSAA measures (Supplementary Fig. 1).

Safety

The safety profile of viltolarsen over the course of the LTE study was acceptable and comparable to that observed in the initial 24-week study. TEAEs were reported by all 16 participants and were primarily categorized as mild or moderate in severity (Table 2). Only one mild TEAE of injection site extravasation (80 mg/kg/week treatment group) was assessed as related to the study drug, which resolved the same day. The most frequently reported TEAEs by preferred term (≥25% of participants) in the LTE study overall were cough, nasopharyngitis, fall, influenza, insect bite, contusion, nasal congestion, vomiting, headache, pyrexia, and rash (Table 2). There were four SAEs reported in three participants and all were categorized by the investigators as unrelated to study medication, including left tibia and fibula fracture, right femur fracture, rhabdomyolysis, and left tibia and fibula fracture. No action was taken with the study drug, and all of these SAEs resolved with patients having recovered. Laboratory data on renal function (including cystatin C) were followed for the whole length of the study, with no clinically significant findings being reported. No participants discontinued the study drug due to treatment-emergent SAEs or AEs, and no deaths occurred during the study.

DISCUSSION

This was an open-label LTE study that assessed the efficacy and safety of viltolarsen for 192 weeks in boys with DMD. The results of timed function tests, such as TTSTAND, TTRW, and TTCLIMB, are key indicators for assessing the progression of

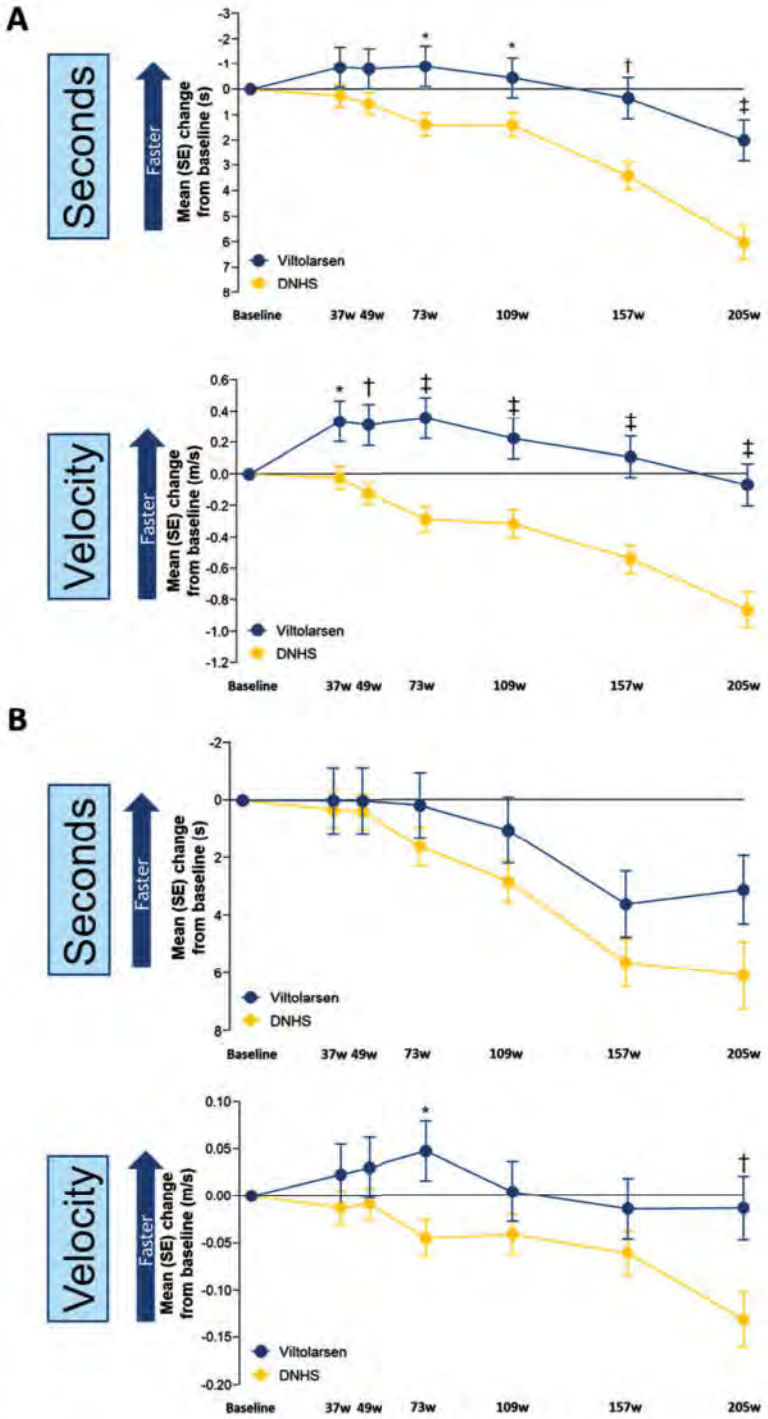

Fig. 3. Timed Function Tests: Change From Baseline vs Natural History for TTRW and TTCLIMB. A. TTRW change from baseline vs natural history controls. B. TTCLIMB change from baseline vs natural history controls. $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P \leq 0.001$. DNHS, Duchenne Natural History Study; s, seconds; SE, standard error; TTCLIMB, time to climb 4 stairs; TTRW, time to run/walk 10 meters; w, weeks. TTRW (seconds) Viltolarsen sample size (n): 16, 16, 15, 16, 16, 14, 14. TTRW (seconds) CINRG DNHS sample size (n): 65, 32, 58, 28, 29, 26, 16. TTRW (velocity) Viltolarsen sample size (n): 16, 16, 15, 16, 16, 14, 14. TTRW (velocity) CINRG DNHS sample size (n): 65, 32, 59, 29, 29, 27, 19. TTCLIMB (seconds) Viltolarsen sample size (n): 16, 16, 14, 16, 16, 14, 13. TTCLIMB (seconds) CINRG DNHS sample size (n): 65, 33, 56, 28, 30, 23, 10. TTCLIMB (velocity) Viltolarsen sample size (n): 16, 16, 14, 16, 16, 14, 13. TTCLIMB (velocity) CINRG DNHS sample size (n): 65, 33, 57, 29, 30, 26, 16.

Table 2
Safety profile of viltolarsen and common TEAEs (Preferred Term in ≥ 25% of Participants)

Participants with	Viltolarsen treatment		Total
	40 mg/kg/wk ($n=8$)	80 mg/kg/wk ($n=8$)	($N=16$)
Any TEAE, *n* (%)	8 (100)	8 (100)	16 (100)
Any drug-related TEAE, *n* (%)	0	1 (13)[a]	1 (6)
Any serious TEAE, *n* (%)	1 (13)	2 (25)	3 (19)
Study drug discontinuation due to TEAE, *n* (%)	0	0	0
Death, *n* (%)	0	0	0
AE, *n* (%)			
Cough	5 (63)	5 (63)	10 (63)
Nasopharyngitis	4 (50)	5 (63)	9 (56)
Insect bite	4 (50)	2 (25)	6 (38)
Rash	2 (25)	4 (50)	6 (38)
Vomiting	3 (38)	3 (38)	6 (38)
Fever	2 (25)	3 (38)	5 (31)
Fall	4 (50)	1 (13)	5 (31)
Headache	3 (38)	2 (25)	5 (31)
Nasal congestion	3 (38)	2 (25)	5 (31)
Influenza	3 (38)	1 (13)	4 (25)
Diarrhea	1 (13)	2 (25)	3 (19)

[a]Assessed as injection site extravasation. AE, adverse event; TEAE, treatment-emergent AE; wk, week.

DMD [16]. These data, combined with the initial 24-week study, provide over 4 years of functional outcomes data—the longest such study and the only one with positive, significant motor function outcomes for an exon 53 skipping therapy [17]. The observed outcomes of maintained clinical performance in timed function tests over the first two years, followed by a significant slowing of disease progression over the next two years, was demonstrated in the viltolarsen-treated participants, whereas the prospectively collected comparator control group showed a more significant functional decline over the entire course of the 4-year study. The differences in reported motor outcomes between viltolarsen and golodirsen, another exon 53 skipping agent with long-term data available, may be associated with the extent of dystrophin rescue, as viltolarsen has shown a mean dystrophin increase in muscle of 6%, whereas golodirsen administration over 48 weeks resulted in dystrophin protein being present at 1% [13, 17].

DMD is a progressive disease with current therapies aiming to delay motor decline for as long as possible, providing meaningful improvement in quality of life. The TTSTAND and TTRW timed function tests in the viltolarsen treatment group showed clear and significant differences over the 4-year study period compared with the CINRG DNHS group, which was matched for key factors, including age, baseline ambulatory ability, steroid use, and geographic location. The TTCLIMB assessment in the viltolarsen treatment group was numerically better (seconds) and significantly better (velocity, weeks 37 and 205) than the CINRG DNHS group, but the overall effect was less pronounced. There may be several reasons for this observation. First, there is greater variability in the TTCLIMB data compared to TTSTAND and TTRW. This may be due, in part, to some boys using a compensation strategy during the TTCLIMB test (eg, using the available handrail to complete the task). Second, fatigue could be a factor since TTCLIMB was not the first test administered. Interestingly, when the seconds measured was transformed to velocity, the viltolarsen-treated group had an essentially flat and stable profile throughout the 205 weeks, whereas the CINRG DNHS group still showed decline, thus indicating a viltolarsen treatment effect.

Viltolarsen was well tolerated in this study, with most of the reported TEAEs being mild or moderate with no deaths or study discontinuations. No treatment-related SAEs and no new or unexpected safety findings with viltolarsen were observed in this LTE study. Most adverse events were consistent with conditions expected in a pediatric population with DMD.

Limitations

Limitations of this study include the small number of participants and the lack of a placebo control arm. With DMD occurring in only approximately 1 : 3600 to 1 : 9300 male births, and only 8%–10% of patients

having DMD who are amenable to exon 53 skipping, [1, 2] there are clear challenges in recruiting large numbers of patients. The small sample size ($N = 16$) in this study is consistent with other studies investigating treatment options for this patient population [13, 17, 18]. The use of a historical group over a placebo arm is less rigorous than a randomized, placebo-controlled study design. However, the CINRG DNHS control group was matched to the viltolarsen group on key criteria, including age, ambulatory ability, glucocorticoid treatment, and geographic location. Additionally, deletion of exons 1–8 and patients amenable to exon 44 skipping, which have milder disease progression, were excluded from the historical control group, allowing for a better match between participants in the LTE study and the CINRG DNHS control group. Finally, it is important to acknowledge that the best comparators in this study are participants with DMD amenable to exon 53 skipping ($n = 9$ in this study). However, recent evidence from the Collaborative Trajectory Analysis Project showed that participant genotypes in DMD studies have a limited effect on motor outcomes, suggesting the viability of trial designs that incorporate genotypically mixed or unmatched controls, supporting the use of mixed genotypes in the control group in this study [19].

CONCLUSIONS

The study outcome of improved motor function vs historical controls, and a favorable safety profile, have been demonstrated in the longest exon 53 skipping therapy trial to date. This is the only study of an exon 53 skipping agent used to demonstrate significant functional benefit over 4 years with comparison to a group-matched, prospectively collected, control group. Based on the efficacy and safety data reported here, combined with the previously reported significant increase in dystrophin levels in these same participants, viltolarsen can be an important part of the treatment strategy for DMD patients who have mutations that are amenable to exon 53 skipping.

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CONFLICTS OF INTEREST

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holds stock in ReveraGen BioPharma outside the submitted work. EPH is also an associate editor of this journal but was not involved in the peer-review process nor had access to any information regarding its peer review. **The Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS)** was supported by grants H133B031118 and H133B090001 from the US Department of Education and National Institute on Disability, Independent Living, and Rehabilitation Research; grant W81XWH-12-1-0417 from the US Department of Defense; grant R01AR061875 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases; and grants from the Parent Project Muscular Dystrophy.

SUPPLEMENTARY MATERIAL

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EXHIBIT K

Journal of Neuromuscular Diseases 10 (2023) 1151–1153
DOI 10.3233/JND-239004
IOS Press

Letter to the Editor

Letter to the Editor: In response to P.R. Clemens et al., *Efficacy and Safety of Viltolarsen in Boys with Duchenne Muscular Dystrophy: Results From the Phase 2, Open-Label, 4-Year Extension Study, and Long-Term Functional Efficacy and Safety of Viltolarsen in Patients with Duchenne Muscular Dystrophy*

Francesco Muntoni[a], Volker Straub[b], Laurent Servais[c] and Eugenio Mercuri[d]
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[d]*Peadiatric Neurology, Catholic University, Rome, Italy*

Published 7 November 2023

Dear Prof Bönnemann and Lochmüller,

We are writing to express our concerns regarding several aspects of two recently published articles in the Journal of Neuromuscular Diseases entitled:

Clemens et al., *Efficacy and Safety of Viltolarsen in Boys with Duchenne Muscular Dystrophy:*

Results From the Phase 2, Open-Label, 4-Year Extension Study [1]

Clemens et al., *Long-Term Functional Efficacy and Safety of Viltolarsen in Patients with Duchenne Muscular Dystrophy*. [2]

These 2 manuscripts are focused on aspects of clinical efficacy of the chronic administration of Viltolarsen in a group of boys affected by Duchenne muscular dystrophy. Viltolarsen is an antisense oligonucleotide designed to induce exon 53 skipping. As this was an open label study, an external clinical comparator, the CINRG cohort, was used to assess the clinical benefit.

For full disclosure, we are 4 academic PIs who recently co-authored a series of manuscripts on another morpholino antisense to induce exon 53 skipping (golodirsen). As academic investigators, we truly welcome competing initiatives that bring new therapies to people affected by DMD, and we are pleased to see that viltolarsen at the doses used (80 mg/kg) was on the whole well tolerated and clearly induced dystrophin protein expression. It is also very good news for the field that viltolarsen

received accelerated approval by FDA, increasing the therapeutic options for people affected by DMD. We need, however, to draw your attention to several inaccurate and potentially misleading statements provided in these manuscripts that had not been identified during the peer review process.

CLAIMS OF CLINICAL EFFICACY

In these manuscripts there are serious shortcomings in the methodology used for comparing the clinical efficacy to the external controls.

Already in the original JAMA Neurology manuscript published in 2020 [3], where the early results of the clinical trial were reported, there were claims of superiority of the treatment arm in comparison with historical controls at week 13. The data matching conducted with the CINRG cohort was imbalanced in relation to various clinical parameters previously demonstrated by several groups including CINRG investigators to play a crucial role in influencing disease trajectories.

The imbalance between the treatment arm and the external CINRG arm is evident: the viltolarsen cohort favorably compared to the CINRG cohort for time to run 10 meters, 6 minute walk test, time to climb 4 steps, making the comparative analysis not robust. In addition, no information on the crucial corticosteroid exposure matching was provided.

The two more recent manuscripts published by the same authors in *Journal of Neuromuscular Diseases* [1, 2] use even less stringent propensity matching criteria between the treated patients and the external controls. Indeed, in these 2 studies, patients were only matched for age, weight, height and BMI, but not for other crucial determinants of clinical severity, further diverging from the accepted methodologies for accurate and transparent clinical matching.

The field has evolved considerably in the 8 years and several peer reviewed publications have clearly identified relevant factors for predicting trajectories compared to these simple demographic parameters [4-8]. In our opinion these omissions challenge therefore the significance of the clinical reported findings.

In our previous manuscript on exploratory clinical efficacy of golodirsen with a genotyped matched external control [9], we used a stringent propensity score matching using age, corticosteroid usage, 6MWT and rise from the floor, parameters that are well recognized to have predictive value in DMD.

While it is very likely that viltolarsen will eventually provide benefit to treated patients, the inappropriate propensity matching and the evolving criteria used in different manuscripts weaken the claim of superiority compared to golodirsen treated patients and complicates interpretation of the efficacy of the viltolarsen findings.

CLAIMS OF SUPERIORITY IN THE PROTEIN PRODUCTION OF THE ADMINISTRATION OF VILTOLARSEN COMPARED TO GOLODIRSEN

In the discussion of the last paper in JNMD, the authors state that “viltolarsen has shown a mean dystrophin increase in muscle of 6%, whereas golodirsen administration over 48 weeks resulted in dystrophin protein being present at 1%”. However, this superiority claim lacks methodological robustness. Indeed, previous collaborative work including FDA regulators and senior authors of the viltolarsen manuscripts had clearly indicated that it was not possible to perform meaningful comparative analysis of western blots performed in different labs as there is no dystrophin standard carried over [10]. Furthermore, we also note that the level of baseline dystrophin concentration in the JAMA Neurology manuscript was considerably higher compared to the one reported in the original golodirsen manuscript [11]. Indeed, in the 2 cohorts of the viltolarsen paper, the baseline dystrophin level was a mean of 0.3% in one of the two cohorts, and 0.6 in the second cohort.

In the original golodirsen manuscript [11] the mean baseline dystrophin level was 0.095% with only a single patient having baseline protein levels above 0.25%, which constitutes the lower limit of detection. The fold increase from baseline would if anything appear to be more favourable for golodirsen compared to viltolarsen, but in view of the differences in methodologies used in the different studies we feel more prudent to conclude that both studies unequivocally demonstrated increased dystrophin production. We think that any comparison with the two products on the basis of these two studies can be misleading.

In conclusion, this population of boys with DMD needs efficacious therapeutic options and viltolarsen appears to provide and additional therapeutic opportunity. This is indeed very good news for the field. However, the entire community needs findings that are reported and interpreted in an accurate and transparent way. The discussion should avoid claims

of superiority that may provide them and/ or the company they represent with a commercial advantage, and journals should pay particular attention for this not to happen. Our patients and colleagues deserve balanced and robust evidence when deciding which therapies to use.

Sincerely,

Francesco Muntoni
Volker Straub
Laurent Servais
Eugenio Mercuri

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EXHIBIT L

Journal of Neuromuscular Diseases 10 (2023) 1155–1157
DOI 10.3233/JND-239005
IOS Press

Reply to the Letter to the Editor

Reply to F. Muntoni et al.: "In response to P.R. Clemens *et al.*, *Efficacy and Safety of Viltolarsen in Boys with Duchenne Muscular Dystrophy: Results From the Phase 2, Open-Label, 4-Year Extension Study, and Long-Term Functional Efficacy and Safety of Viltolarsen in Patients with Duchenne Muscular Dystrophy*

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Published 7 November 2023

Dear Drs. Bonnemann and Lochmuller,

We appreciate the opportunity to respond to the comments on our publications on viltolarsen and to have this exchange with Drs. Muntoni, Straub, Servais and Mercuri [7]. Our colleagues compare/contrast their industry-sponsored program of golodirsen, with our industry-sponsored program of viltolarsen (different exon 53 skipping medications in DMD patients, both approved for use in DMD by FDA in the USA, with viltolarsen also approved by PMDA in Japan; all under the accelerated surrogate biomarker pathway).

We strongly disagree with their statement that our publications contained "several inaccurate and potentially misleading statements that had not been identified during the peer review process."

First, under their "Claims of Clinical Efficacy" heading, we all recognize that clinical efficacy is proven by double-blind, placebo-controlled trials. Neither the golodirsen nor viltolarsen programs have as yet reported placebo-controlled efficacy trials. Comparisons of trial participants treated in open-label studies to external natural history comparators only provide suggestive evidence. As we clearly state in the publications cited, limitations of our studies include "the small number of participants and the lack of a placebo control arm," and "The use of a historical group over a placebo arm is less rigorous than a randomized, placebo-controlled study design."

Second, Muntoni and colleagues point out differences between the viltolarsen and golodirsen programs related to statistical procedures for matching of the limited number of participants in these

clinical trials to external, natural history comparators. The viltolarsen-treated patients from our open label trial ($n = 16$) were group-matched to external comparators from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS) [4]. This differs from the patient-matching methodology used in studies in which Muntoni and colleagues were involved. The group-matched external comparator cohort, as described in the viltolarsen manuscripts, is entirely appropriate; it is simply different from the strategy taken by Muntoni and colleagues to generate an external comparator group for an open label study. Each of the different methods used can have pros and cons, but to simply say that the method chosen for the viltolarsen studies challenges the integrity of the work, is not a valid criticism.

For the viltolarsen program, the major study eligibility criteria used for the viltolarsen cohort was matched to the external comparator group (CINRG DNHS dataset) and included glucocorticoid use, age, ambulatory ability at baseline, and geographic location. It is very important to note that the statement by Dr. Muntoni and colleagues that 'no information on the crucial corticosteroid exposure matching was provided' is misleading and matching for glucocorticoid use was in fact described in each of the three papers cited. Further, Dr. Muntoni's statement that 'evolving criteria' were used across the studies is not correct. The exact same cohort of patients from the CINRG historical control group were utilized in all three papers across the four-year time-period, further serving to increase the robust nature of these analyses. In the golodirsen study Muntoni and colleagues used an alternative approach of per-patient matching from natural history data sets [5]. As expected, this leads to a much smaller external comparator group studied in long-term golodirsen-treated subjects (control group $n = 19$; [5]), compared to our long-term study (control group $n = 65$; [2]). Clearly, smaller numbers can lead to greater challenges with interpretation.

Third, Muntoni and colleagues then turn to criticisms of interpretation of dystrophin protein data from muscle biopsies in the peer-reviewed study of viltolarsen published in *JAMA Neurology* [3]. Specifically, Muntoni and colleagues cite a sentence in the Discussion of our later Clemens et al. 2023 publication [1], where we simply cite data from other published, peer-reviewed papers. In the initial golodirsen open label trial, the authors report an increase in dystrophin to 1% normal levels after treatment [6], whereas we found a mean viltolarsen-related increase in dystrophin of 6% normal levels [3]. Both the viltolarsen and golodirsen studies used standard Western blot methods. The viltolarsen program had a standardized collection of samples followed by Western blot analysis at a single laboratory in a blinded fashion using an honest broker approach to have paired samples on the same gel. Furthermore, a rigorous, consistent standard control series was included on each gel as discussed with FDA. In the Discussion section of the Clemens 2023 paper [1], we included the previously published results for golodirsen, which seems appropriate to us. Because there is no head-to-head comparison of golodirsen and viltolarsen, the reader will need to draw their own comparative conclusions by reading the manuscripts from both groups. Muntoni and colleagues seem focused on the difference in low baseline dystrophin levels in the golodirsen study (mean baseline 0.09% of normal in Frank et al. 2020 [6]) as compared to the low baseline dystrophin levels in the viltolarsen study (mean baseline 0.45% of normal in Clemens et al. 2020 [3]). The baseline dystrophin levels reported in both studies are generally below the lower limits of quantitation of the Western blot assays utilized, and highly unlikely to be relevant to any data interpretation of drug effect. Furthermore, describing an increase as a multiplication of an extremely low, and likely not measurable, baseline value has the potential to be deceptive. Absolute values of newly created dystrophin in skeletal muscle are essential in these patients, which is the data that we have shown.

We encourage readers to refer to the original peer-reviewed publications of both viltolarsen and golodirsen and to come to their own scientific conclusions. We believe that the concerns voiced by Dr. Muntoni and colleagues do not have an impact on the interpretation of these publications.

We share the thoughts expressed by Dr. Muntoni and colleagues, and indeed all researchers, patients with DMD and their families, that the therapeutic developments for DMD have been most encouraging 'good news' in recent years. We are confident that we have reported 'balanced and robust evidence' and we will continue to do so.

Sincerely,

Paula R. Clemens, MD
Professor and Vice Chair
Department of Neurology
School of Medicine

University of Pittsburgh

Eric P. Hoffman, PhD
Associate Dean
Research and Research Development
School of Pharmacy and Pharmaceutical Sciences
Binghamton University

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EXHIBIT M

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Transcript of Jonathan B. Strober, M.D.

Date: November 16, 2023
Case: Nippon Shinyaku Co., Ltd. -v- Sarepta Therapeutics, Inc.

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www.planetdepos.com

both ends, and so the protein can actually work. 03:03:11

And then if it's a shortened protein, a 03:03:15

lot of times the body will just get rid of it so 03:03:19

there's no evidence that there's a protein at all. 03:03:22

And so when the muscle is held together 03:03:25

better, there's less injury to the muscle and less 03:03:27

loss of muscle over time. 03:03:31

Q So as you understand it, both VYONDYS and 03:03:33

VILTEPSO are resulting in at least some increased 03:03:36

dystrophin production; is that fair? 03:03:40

A Yes. 03:03:42

Q Do you agree that both VYONDYS and 03:03:43

VILTEPSO have similar safety profiles? 03:03:45

A Yes. 03:03:49

Q I'm trying to count my exhibits here. 03:04:11

ATTORNEY VINK VENEGAS: I think you're on 03:04:13

Number 6. 03:04:15

ATTORNEY O'QUINN: That seems right. 03:04:18

Q (BY ATTORNEY O'QUINN) I'm going to mark as 03:04:19

Exhibit 6, a production document in this case 03:04:20

bearing beginning Bates Number NS 00143179. 03:04:22

(Exhibit 6 was marked for identification 03:04:29

and is attached to the transcript.) 03:04:29

Q (BY ATTORNEY O'QUINN) And this document is 03:04:44

entitled -- it's dated December 8, 2020. The -- 03:04:48

clear record. 03:50:23

Is it fair to say the FDA agrees that a comparison should not be made of dystrophin values following treatment with VYONDYS 53 and VILTEPSO? 03:50:26 03:50:28 03:50:31

A Correct. 03:50:36

Q Staying on this exhibit, if you could go with me to the page ending in 6988, the "Clinical Studies" section. 03:50:41 03:50:44 03:50:52

Do you see that? 03:50:54

A Yes. 03:50:54

Q Look at the very last sentence on the page. This paragraph is discussing Study 1, Part 2 of the clinical trials for VYONDYS. 03:50:59 03:51:01 03:51:09

Do you agree with that? 03:51:13

A Yes. 03:51:14

Q The last sentence states: 03:51:14

> Mean dystrophin levels increased from 0.1 percent of normal at baseline to 1.02 percent of normal by Week 48 of Study 1, Part 2. 03:51:17 03:51:17 03:51:21 03:51:24 03:51:27

Do you see that? 03:51:29

A Yes. 03:51:30

Q So you agree the baseline here was 0.1 percent of normal -- 03:51:30 03:51:32

Q It says:
Among golodirsen-treated patients, FVC percentage P declined by 8.4 percent over three years of treatment from a mean FVC percentage P of 92.7 percent at baseline to 83.8 percent at Week 144, correct? 04:01:37 04:01:37 04:01:38 04:01:42 04:01:45 04:01:47 04:01:48 04:01:52
A Correct. 04:01:54
Q What is FVC percentage P? 04:01:55
A Forced Vital Capacity. 04:01:59
Q So that's a pulmonary measurement? 04:02:01
A Yes. 04:02:04
Q Do you know how elevated a DMD patient's dystrophin level has to be to make a functional difference? 04:02:39 04:02:44 04:02:47
ATTORNEY VINK VENEGAS: Objection to form. 04:02:48
A That is a question that is continuously discussed, and nobody really knows. 04:02:50 04:02:53
Q (BY ATTORNEY O'QUINN) If we look at your reply report, you state in the last sentence of that paragraph: 04:02:59 04:03:02 04:03:35
The relative change in dystrophin production following VILTEPSO and VYONDYS treatment -- 04:03:35 04:03:40 04:03:42

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) **DEMAND FOR JURY TRIAL**
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff/Counter Defendants.	[redacted] [redacted]

PLAINTIFF'S RESPONSE TO SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S MOTION *IN LIMINE* NO. 2 TO EXCLUDE EVIDENCE OR ARGUMENT THAT NS'S COMMERCIAL PRODUCT (VILTEPSO) PERFORMS BETTER THAN SAREPTA'S COMMERCIAL PRODUCT (VYONDYS 53)

Amanda S. Williamson (admitted *pro hac vice*)
Christopher J. Betti (admitted *pro hac* vice)
Krista V. Venegas (admitted *pro hac* vice)
Wan-Shon Lo (admitted *pro hac vice*)
Maria E. Doukas (admitted *pro hac vice*)
Zachary Miller (admitted *pro hac vice*)
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Attorneys for Plaintiff/Counterclaim Defendant Nippon Shinyaku Co., Ltd. and Counterclaim Defendant NS Pharma, Inc.

Dated: April 25, 2024

Sarepta's motion to exclude evidence and arguments that NS's VILTEPSO is superior to VYONDYS 53 is a trojan horse—Sarepta's arguments are a thinly veiled attempt to block NS from establishing that its product is a suitable alternative to VYONDYS 53 and impair NS's effort to establish it would have made profits lost to Sarepta's infringing VYONDYS 53 product. NS has no intention of making head-to-head superiority claims. Rather, establishing VILTEPSO's strong clinical profile for exon 53 amenable patients, its efficacy, and its safety is probative and admissible to show that, in the but-for world, VYONDYS 53 customers would have chosen VILTEPSO. In fact, NS—whose NS Patents' claimed invention is VYONDYS 53's active ingredient—plans to actively show that ***both*** products help exon 53-amenable patients.

Sarepta asks the court to exclude the very same type of evidence Sarepta itself relies on—VYONDYS 53's clinical profile—to argue that it is entitled to lost profits. NS should be allowed to do the same for VILTEPSO's strong clinical profile to show that NS is entitled to lost profits. Because Sarepta intends to introduce the same type of evidence for its product, such evidence cannot be unfairly prejudicial, and the Court should deny Sarepta's Motion.

I. VILTEPSO's Strong Clinical Profile Is Relevant to Lost Profits.

Sarepta attempts to limit NS to arguing that customers in the but-for world would have chosen VILTEPSO simply because VILTEPSO and VYONDYS 53 are both "FDA-approved, safe and effective, and compete for the same patients." Mot. At 1. Sarepta argues the clinical profiles of VILTEPSO and VYONDYS 53 are irrelevant. Not so. Evidence related to the clinical profiles of both products is necessary to show that NS's VILTEPSO is a suitable alternative to Sarepta's VYONDYS 53 that customers would have chosen. *See Rite-Hite Corp. v. Kelley Co.*, 56 F.3d 1538, 1548 (Fed. Cir. 1995) (affirming lost profits award where plaintiff's non-patent practicing product was nevertheless an "acceptable substitute" for the infringing product). As NS Pharma's Mr. Gardner Gendron explains, as a practical matter, NS Pharma's best path to acquiring new

patients has been "[s]elling the benefits of the product, its intent to treat, clinical profile, and safety profile." Ex. 1 at 132:8-12; *see also id.* at 184:13-17 (noting "our clinical profile and effectiveness in delivering a message" as "factors" in VILTEPSO's "strong performance").

NS Pharma's practical observations comport with opinions from both parties' clinical experts. NS's clinical expert, Dr. Jonathan Strober, explains that clinicians use data from clinical trials and published papers to make prescribing decisions. Def. Mot. in Lim. Ex. D ¶ 8. Likewise, Sarepta's clinical expert, Dr. Stanley Nelson, provides a detailed discussion regarding VYONDYS 53's favorable clinical profile—including the western blot data showing VYONDYS-53 induced increase in dystrophin protein. Ex. 2 ¶¶ 45-54. There is no reason why ***only*** Sarepta—and not NS—should be permitted to highlight its product's favorable clinical profile to prove lost profits.

Sarepta's complaint regarding supposed comparisons is of its own making. After NS's damage expert, Mark Hosfield, offered his lost profits opinions, (Ex. 3 at 81, 108), Sarepta's damages expert, John Jarosz, critiqued him for allegedly failing to account for the "natural ramp-up process" needed for VILTEPSO to capture lost VYONDYS 53 vials. Ex. 4 ¶¶ 118-125. In rebuttal, Mr. Hosfield noted key differences in each product's commercial launch indicating that VILTEPSO's ramp-up would have been equivalent or better than VYONDYS 53's. NS Pharma "anticipated the possibility" of a much earlier launch because the FDA initially ***declined*** to approve VYONDYS 53. Ex. 5 at 5. And while Sarepta had to combat the FDA's public statements initially questioning VYONDYS 53's clinical benefit, the "dystrophin levels induced by VILTEPSO [redacted]." *Id.*

Sarepta's argument that NS's patents do not cover VILTEPSO is inapposite. A patentee may recover lost profits on a product that is not the patented invention so long as the "infringement in fact caused the patentee's lost profits." *Rite-Hite*, 56 F.3d at 1548-49. Dr. Strober explained that

"VILTEPSO and VYONDYS 53 are directed at the same patient population . . . and have the same general mechanism of action." Ex. 6 ¶¶ 61-62. As Mr. Hosfield explains, VILTEPSO competes in the market with VYONDYS 53. Ex. 3 at 60-62.

II. Evidence Regarding VILTEPSO's Clinical Profile of VILTEPSO Is Reliable.

Sarepta's argument that a comparison of VILTEPSO and VYONDYS 53 is "not based on reliable principles and methods" lacks merit—it did not move to exclude either Mr. Hosfield's or Dr. Strober's opinions. *See* D.I. 395. Moreover, the clinical data of VILTEPSO and VYONDYS 53 will not be used to prove that one product is better than the other. Rather, the clinical profiles may be used to show how prescribing clinicians—who have access to and routinely review such data—make prescribing decisions. *See* Def. Mot. in Lim. Ex. D ¶ 8.

That the FDA does not allow NS to ***market*** VILTEPSO as superior over VYONDYS 53 is immaterial. In *Hill v. GEO Group*, the court excluded expert testimony because the FDA had found the test the expert used to be unreliable. 2021 WL 6053783, at *5-6 (W.D. La. Dec. 21, 2021). Here, the FDA approved both VILTEPSO and VYONDYS 53 based on the clinical trial data whose methodology it reviewed. Sarepta cannot credibly argue that such results are "unreliable."

* * *

Sarepta's concerns regarding a "mini-trial" on product superiority is unfounded and an excuse to try to impair NS's lost profits analysis. The clinical profiles, efficacy, and safety of both VILTEPSO and VYONDYS 53 directly underlie the parties' lost profits analysis. Mot. at 3. The only risk of unfair prejudice would be allowing Sarepta to tout its product's efficacy, while precluding NS from doing the same. While NS does not intend to argue that VILTEPSO is head-to-head superior to VYONDYS 53, NS should be able to show evidence related to VILTEPSO's clinical profile—just as Sarepta will with VYONDYS 53. Accordingly, the Court should deny Sarepta's Motion.

Dated: April 25, 2024

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

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Exhibit 1 to NS's Response to Sarepta's MIL No. 2

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant
C.A. No. 21-1015 (GBW)

SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. AND NS PHARMA, INC., Plaintiff/Counter-Defendants.

ATTORNEYS' EYES ONLY
Videotaped Deposition of NIPPON SHINYAKU CO., LTD., AND NS PHARMA, INC.,
By and Through Designated Representative,
GARDNER GENDRON,
and In His Individual Capacity
New York, New York
Tuesday, July 11, 2023
9:35 A.M.

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Job No.: 494164
Pages: 1 - 220
Reported By: Anita M. Trombetta, RMR, CRR

Videotaped Deposition of GARDNER GENDRON, held at the offices of:

Morgan Lewis & Bockius LLP (NY)
101 Park Avenue
New York, NY 10178-0060
212.309.6000

Pursuant to notice, before Anita M. Trombetta, RMR, CRR, Notary Public in and for the State of New York.

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A P P E A R A N C E S

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----------I N D E X----------

WITNESS
GARDNER GENDRON
EXAMINATION BY Page
MR. O'QUINN 9

----------E X H I B I T S----------

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P R O C E E D I N G S

THE VIDEOGRAPHER: This begins media number one in the video recorded deposition of Gardner Gendron, in the matter of Nippon Shinyaku, want Co., LTD. vs. Sarepta Therapeutics Inc., in the United States District Court for the District of Delaware. The case number is 21-0115 -- excuse me, 21-1015 (GBW.)

Today's date is July 11, 2023, and the time on the video monitor is 9:35 A.M. The videographer today is Kevin Gonzalez, representing Planet Depos. This video deposition is taking place at 101 Park Avenue, New York, New York 10178.

Would counsel please voice identify yourselves and state whom you represent, beginning with the noticing attorney.

MR. O'QUINN: Ryan O'Quinn from Finnegan LLP representing defendant/counterclaim plaintiffs Sarepta Therapeutics and the University of Western Australia.

MS. WILLIAMSON: Amanda Williamson from Morgan Lewis representing Shinyaku and NS Pharma.

THE VIDEOGRAPHER: Thank you, counsel.

The court reporter today is

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Anita Trombetta, representing Planet Depos. The witness can now be sworn in.
THE VIDEOGRAPHER: You may proceed, counsel.
GARDNER GENDRON,
called as a witness, having been duly sworn by a Notary Public, was examined and testified as follows:
EXAMINATION BY
MR. O'QUINN:
Q Good morning, Mr. Gendron.
A Good morning.
Q Have you ever been deposed before?
A No.
Q Congratulations on joining the club. I'm going to ask you a few questions today. If you have any issues with my question or want me to clarify, please let me know. If you answer my question, I'll assume that you understood it as it was asked. Is that fair?
A Yes.
Q And the court reporter needs verbal answers for the record: Yes, no. We can't nod our head, shake our head, etc., is that fair?
A Yes.

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Q Your counsel will likely object throughout the day, but unless she instructs you specifically not to answer, I'd like to get an answer to the question I've asked, correct? Is that okay?
A Yes.
Q I'll aim to take a break approximately once an hour. You're welcome to take breaks at different times if you'd like; just let me know, I'll grant you that. I'd just ask that any question that's pending be answered before we go on break. Is that fair?
A Yes.
Q Is there any reason that you can't answer the questions I'm about to ask you fully and truthfully?
A No.
(Gendron Exhibit 1, Notice of 30(b)(6) Deposition, marked for identification.)
Q I'm going to mark as Gendron Exhibit 1, the Notice of 30(b)(6) Deposition on Plaintiffs. Have you seen this document before, Mr. Gendron?
A I don't recall.
Q Do you understand that you're here today to -- in part, to give corporate testimony on

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behalf of Nippon Shinyaku Limited and for NS Pharma?
A Yes.
Q And do you understand that as part of that responsibility, you've been designated to testify on particular topics?
A Yes.
Q Okay. If you could turn with me to topic 48, which is on Page 14 of the document. Do you see topic number 48, Mr. Gendron?
A Yes.
Q And it's long so I won't read it into the record. But are you prepared to testify today on behalf of Nippon Shinyaku and NS Pharma on topic 48?
MS. WILLIAMSON: I'll just object to the scope of the designation. He's designated to talk on this topic as to the United States, but not any ex-U.S.
MR. O'QUINN: Understood.
A Yes.
Q What did you do to prepare for topic number 48 today, Mr. Gendron?
A I had several meetings with the attorneys and reviewed documents.

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Q Which attorneys did you meet with?
A Amanda and her Morgan Lewis co-attorneys.
Q How many meetings did you have?
A I don't recall the exact number. More than four.
Q Were all of those in person or were some of them online?
A So that's -- can you rephrase the question?
Q Were the meetings that you had with the attorneys face-to-face, in person, or online, like on Zoom, something like that?
A Not all meetings were face-to-face.
Q You said you reviewed documents. Did you review any documents to prepare other than the documents that counsel provided you?
A No.
Q Did you speak to anyone else other than your attorneys in order to prepare?
A Yes.
Q Who did you speak with?
A Taro Tsutsumi, the head of finance.
Q Anyone else?
A No.
Q Did any of the documents you reviewed to

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about earlier?
A Yeah.
Q Has NS Pharma ever done any clinical studies in female Duchenne patients?
MS. WILLIAMSON: Objection. Lacks foundation.
A Not to my knowledge.
Q The third factor on this slide is "[redacted] an the U.S. price, correct?
A Yes.
Q [redacted]

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A My understanding is Vyondys, Amondys, and Exondys were all the same price.
Q [redacted] There's different break points. So at some points Vyondys, Amondys, and Exondys can be less expensive, still, based on when the break of the vial is.
Q What size are the vials of Viltolarsen that NS Pharma sells?
A I don't recall.
Q Do you recall the dose that they are approved at, that Viltolarsen is approved at in the U.S.?
A Yes.
Q What is that?
A 80 milligrams per kilogram.
Q "[redacted]

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[redacted] Do you see that?
A I do. That's what it says.
Q How did NS Pharma come to understand that from payors?
MS. WILLIAMSON: Objection to foundation.
A We did payor research.
Q Is the same thing true for the next bullet, "[redacted] ?
A Ask the question again?
Q Did NS Pharma's [redacted]
A At that point in time there were many pressures, as you say, downward. That was one of the potential downward pressures on [redacted]
Q And the next bullet point says, "[redacted] " correct?
A That's what it says, yes.
Q And then "[redacted]

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[redacted] " correct?
A Yes.
Q Did NS Pharma believe that its best path to acquiring patients would be to [redacted] ?
A No.
Q What did NS Pharma believe its best path would be to acquiring patients?
A Selling the benefits of the product, its intent to treat, clinical profile, and safety profile.
Q Does patient acquisition refer to acquiring newly diagnosed patients, or does it refer to inducing patients to switch that were already on a Sarepta therapy?
A New to therapy is -- can be from any -- can be naive or a switch.
(Reporter clarification.)
A From a naive patient, not on therapy, or a switch.
(Gendron Exhibit 17, Document Bearing Bates Number NS97081, marked for identification.)
Q I'm going to mark as Exhibit 17 a document bearing Bates number NS97081. Have you seen this

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A To celebrate the success of the past year and then set strategy and tactics for the future year.
Q If go to the 27th slide in this presentation, which ends in Bates number 1953. There's reference here to a task force relating to internal corporate culture, correct?
A Yes.
Q There's reference to a [redacted]. What is that?
A It's a term of a [redacted] call that's held.
Q And does GG represent your initials?
A Yes.
Q Why was the [redacted] being referred to here successful?
A The field folks [redacted] call from HQ staff.
Q If you go to slide 31, ending in 1957, please. There's four identified areas for focus here, one of which is identify areas, correct?
A Yes.
Q So if we move to slide 35, which ends in 1961, this slide is entitled "Identified Areas." So what -- what is this listing? Are these issues

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that the team has identified that need to be worked on?
A This is areas that a few people on a task force identified as creating better culture in an organization moving forward.
Q The first bullet point there says, "[redacted]."
Do you see that?
A Yes.
Q Was there a feeling leading into this meeting that NSP was [redacted]?
A I mean, it's a very broad statement. No.
Q Who is [redacted]?
A [redacted] is another manu-- another manufacturer within Duchenne. [redacted]
Q The third bullet point down says, "Be [redacted]" And the example given is "[redacted]."
Do you know what that means?
A I don't. This is, like, a white board session. I don't know.
Q I'd like to go to slide 48, which ends in Page 1974, please. Listed here are the national

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account directors' 2022 objectives, correct?
A Yes.
Q And the first bullet point there is, "[redacted]" correct?
A Yes.
Q Is it -- was it NS Pharma's goal, as of 2022, to be number one in the Exon 53 market?
A Could you restate the question?
Q Did NS Pharma intend for Viltepso to be the number one product in the Exon 53 market?
A In 2022?
Q Yes.
A It was a goal, yes.
Q Is it still a goal today?
A Yes.
Q What's [redacted]?
A Versus?
Q Just the Exon 53 market.
A And what products are in that?
Q How does NS Pharma define that market?
A I guess our [redacted].

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Q With which drug having [redacted]?
A Golodirsen.
Q Is that where NS Pharma believed the [redacted], three years after launch?
A We actually thought it would be l[redacted] [redacted] in the exact same label granted from the FDA.
Q So you consider [redacted] as of today?
A I think it's a strong performance.
Q What factors do you attribute to that strong performance?
A Our clinical profile and effectiveness in delivering a message to key opinion leaders across the nation.
Q Go to slide 50, which is on the page ending in 1976, please. This slide is, "[redacted]" and it lists four [redacted] spanning in time between November 2019 and August 2020, correct?
A Yes.
Q For [redacted] there were

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Output." Do you know whether it was internal research at NS Pharma or research conducted by a third party?

A That message -- that question would be better suited for Stephen Sudavar, the head of marketing.

(Gendron Exhibit 44, Document Bearing Beginning Bates Number NS96087, marked for identification.)

Q I'm going to mark as Exhibit 44 a document beginning Bates number NS96087. It doesn't look like this is listed in Mr. Sudavar's numerical list, but it is listed in the attachment list in the -- in the email header as "Viltepso Viltolarsen Approval Key Messages Q&A," dated August 12th, 2020.

Have you seen this document before?

A (Document review.)

I have seen this before.

(Gendron Exhibit 45, Launch Plan with Beginning Bates Number NS96093, marked for identification.)

Q I'm going to mark as Exhibit 45 a document beginning Bates number NS96093. Do you understand this now to be the initial Viltepso launch plan,

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as addressed in number five of Mr. Sudavar's list to Mr. Kimura?

A Yes.

MR. O'QUINN: Okay. I don't have any more questions for you, Mr. Gendron. I think we're going to need some more testimony at some point on the stretch forecast documents. We didn't find that document in the production other than the document I just showed him, and he said that he needed more material to speak to it.

MS. WILLIAMSON: Well, we can take that under advisement. I understand you're refusing to produce your long range plan, so when you're --

(Reporter clarification.)

MS. WILLIAMSON: -- we can consider producing additional forecast materials.

MR. O'QUINN: I think your understanding is incorrect, based on the meet and confer we were both on on Friday. We can talk offline.

MS. WILLIAMSON: I have no questions.

THE VIDEOGRAPHER: This marks the end of the deposition of Gardner Gendron. We are going off the record at 6:04 p.m.

(Time Noted: 6:04 P.M.)

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ACKNOWLEDGMENT OF DEPONENT

I, GARDNER GENDRON, do hereby acknowledge that I have read and examined the foregoing testimony and the same is a true, correct, and complete transcription of the testimony given by me and any corrections appear on the attached errata sheet signed by me.

_____ _____

(SIGNATURE) (DATE)

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CERTIFICATE OF SHORTHAND REPORTER-NOTARY PUBLIC

I, ANITA M. TROMBETTA, RMR, CRR the officer before whom the foregoing deposition was taken, do hereby certify that the foregoing transcript is a true and correct record of the testimony given; that said testimony was taken by me stenographically and thereafter reduced to typewriting under my direction; that reading and signing was requested ; and that I am neither counsel for, related to, nor employed by any of the parties to this case and have no interest, financial or otherwise, in its outcome.

IN WITNESS WHEREOF, I have hereunto set my hand and affixed my notarial seal this 13th day of July, 2023.

My commission expires: 10.07.2025

ANITA M. TROMBETTA, RMR, CRR

Exhibit 2 to NS's Response to Sarepta's MIL No. 2

THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (GBW) [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

OPENING EXPERT REPORT OF STANLEY NELSON, M.D.

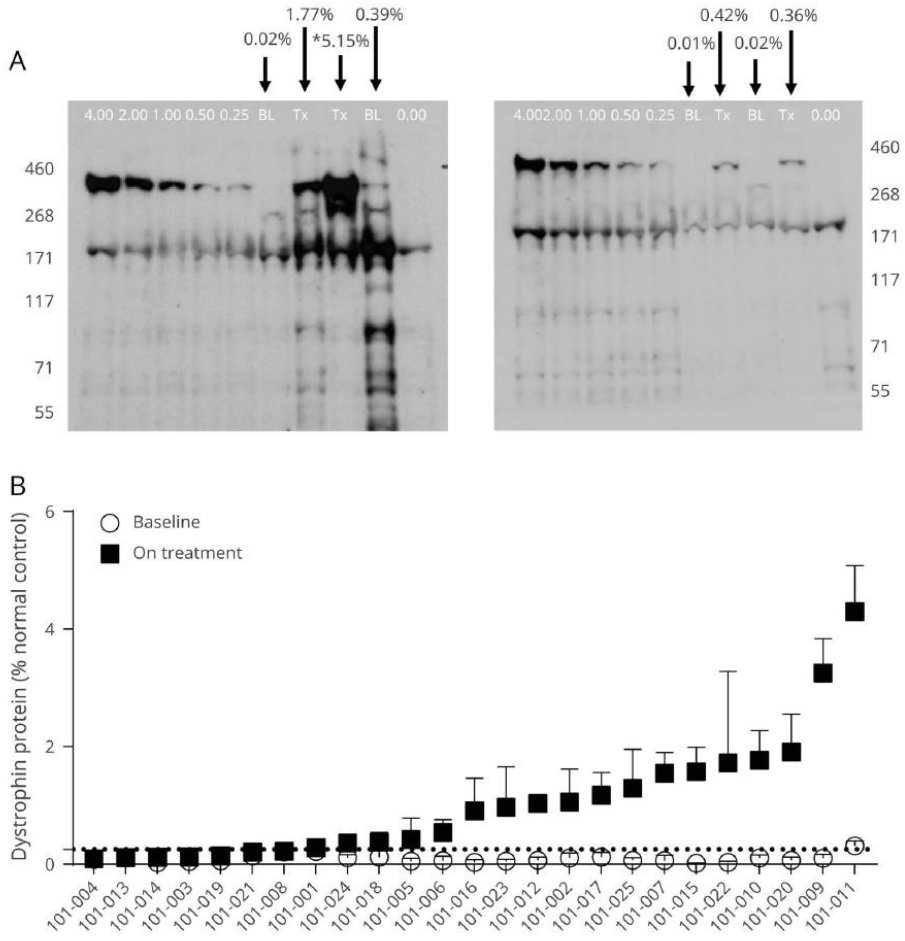
[redacted]

44. No serious treatment-emergent adverse events were reported. Frank 2020 at e2277. Moderate treatment adverse events were reported in 2 patients: *Staphylococcus aureus* infection of the Port-A-Cath and pyrexia. *Id.* The authors of Frank 2020 noted that the treatment-emergent adverse events were "consistent with what would be expected in a pediatric DMD population." *Id.*

45. As reported in Frank 2020, the golodirsen-induced dystrophin increase over baseline was a significant increase and an approximately 16-fold increase in dystrophin. Frank 2020 at e2278. "Muscle biopsy specimens were collected from one biceps brachii muscle at baseline and from the contralateral muscle at week 48 using an optimized, standardized surgical procedure developed to avoid technical issues previously experienced during other studies in the field." Frank 2020 at e2273. Moreover, Western blots were executed according to validated methodology and "[d]ystrophin levels of treatment-blinded samples were calculated from a 5-point standard curve ranging from 0.25% to 4%." *Id.* at e2274 (citing Charleston 2018[9]). "Reported dystrophin levels were the average value of both biological replicates and 2 technical gel replicates for each sample result." *Id.* The Western blot data is shown in the figures below:

[9] Jay S. Charleston et al., *Eteplirsen treatment for Duchenne muscular dystrophy*, 90 NEUROLOGY e2146 (2018) ("Charleston 2018").

[redacted]



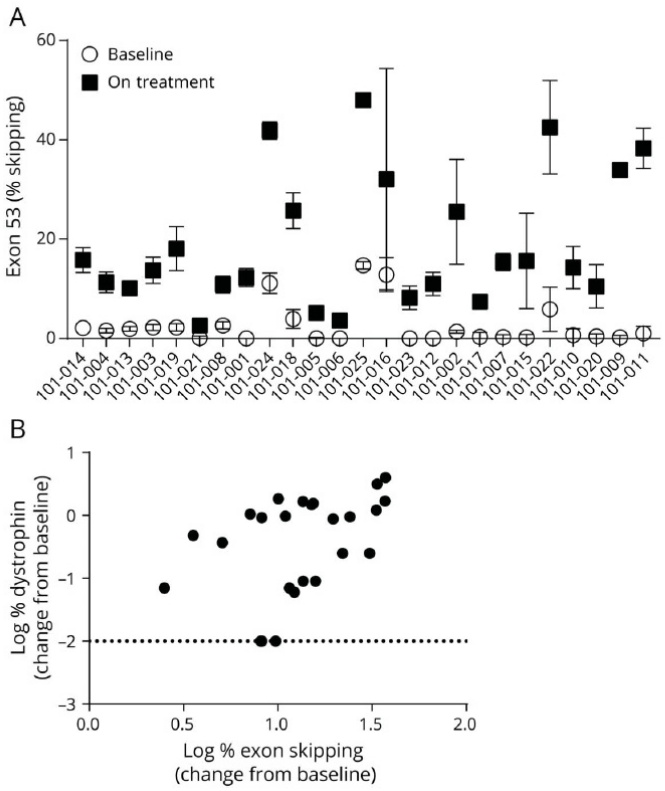
(A) Western blot examples performed with baseline (labeled as BL) and on treatment (Tx) paired samples from 4 patients. Numbers above Tx gel lanes indicate the percent normal control dystrophin, calculated from the standard curve on each blot (lanes denoted with 4%, 2%, 1%, 0.5%, 0.25%). In both panels, lane 0 represents baseline untreated DMD control tissue with no normal control lysate. Arrows and values above gel indicate the percent normal dystrophin measured for the indicated lane. (B) Western blot data shown as averaged dystrophin percent of normal for each individual patient at baseline (open circles) and at part 2, week 48, (solid squares), with dystrophin levels on y-axis presented as linear values. *Sample reading was above the upper limit of quantification.

Frank 2020 at e2274, Figures 2A, B.

46. While the primary biological endpoint in Part 1 of the study was the blinded change from baseline in dystrophin protein levels at week 48 as measured by Western blot, "secondary biological endpoints were evaluation of exon 53 skipping, as measured by RT-PCR, and dystrophin sarcolemmal localization assessed using histochemistry (level of evidence IV)." Frank 2020 at e2273.

47. The mean percentage of exon skipping for all patients increased from 2.590% (SD, 4.0864%; range, 0.00%-14.69%) at baseline to 18.953% (SD, 13.2245%; range, 2.62%-48.03%) at week 48, representing a 28,897-fold increase (SD, 39.36763; range, 2.59-150.36) in exon skipping (shown in the figure below). Frank 2020 at e2278.

[redacted]



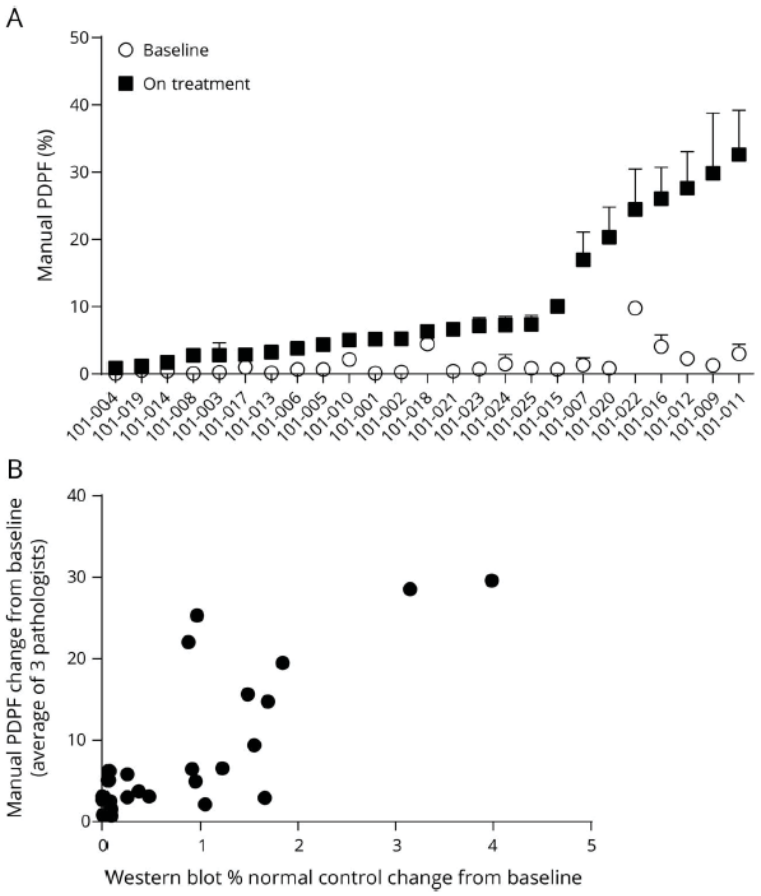
(A) Treatment with golodirsen demonstrates an increase in skipping of exon 53 in dystrophin mRNA. Percent exon 53 skipping for individual patients at baseline (open circles) and on treatment (filled squares). Data represent mean ± SD values for 4–8 replicates. (B) Positive correlation between percent exon 53 skipping and production of dystrophin protein. Percent exon 53 skipping change from baseline was plotted against the change in dystrophin protein from baseline, as measured by Western blot (Spearman *r* correlation coefficient: 0.500; $p = 0.011$).

Frank 2020 at e2275, Figures 3A, B.

48. A significant, positive correlation between exon skipping and *de novo* dystrophin protein expression was observed with a Spearman r correlation coefficient of 0.500 (p = 0.011). Frank 2020 at e2278; *id.* at Fig. 3B.

49. Assessment of percentage dystrophin-positive fibers ("PDPFs") were executed by 3 trained pathologists. Frank 2020 at e2275. "PDPF scoring indicated that weekly treatment of patients with golodirsen at week 48 resulted in a significant increase in positive dystrophin fibers ($p < 0.001$). The mean baseline level for scoring PDPF was 1.430% (SD, 2.042; range, 0.06%–9.75%), whereas mean scoring PDPF at week 48 was 10.471% (SD, 10.102; range, 0.87%–32.59%), a mean per patient 13.461-fold increase (SD, 11.9171; range, 1.88–49.67)." Frank 2020 at e2278. This data is shown in the following figure:

[redacted]



(A) Baseline values of PDPF for each patient are shown as open circles and part 2, week 48, intensity is shown as solid squares. This graphical representation provides a ready way to visualize relative changes in each patient. Data represent the mean of 3–4 replicates with SD bars. (B) Western blot protein change from baseline is plotted on the x-axis and percent dystrophin-positive fiber change from baseline as assessed by manual scoring is plotted on the y-axis. Spearman analysis shows a significant correlation ($p < 0.001$; $r = 0.663$). Each point represents a single patient.

Frank 2020 at e2277, Figures 5A, B.

50. "A positive correlation and linear relationship between dystrophin protein as measured by Western blot and dystrophin localization to the membrane (PDPF) was observed with a Spearman correlation coefficient of 0.663 ($p < 0.001$)." Frank 2020 at e2278; *id.* at Figure 5B.

51. As explained in Frank 2020:

> Our findings demonstrated the robust pharmacologic activity of golodirsen using 3 independent, complementary methods. All 25 patients had an increase in skipping of exon 53, demonstrating clear evidence of target engagement by golodirsen. The primary biological endpoint of the study was achieved, as statistically significant increases of approximately 16-fold over baseline were observed in de novo dystrophin protein expression as measured by Western blot at week 48, with a mean of 1.019% of normal and a range across patients of 0.09%-4.30%. The de novo dystrophin protein correctly localized to the sarcolemma with a significant increase in mean change in PDPF from baseline to 10.471% for a mean increase of 13,461-fold. The consistency of the dystrophin response measured by the complementary

[redacted]

> assays and the positive correlation between exon skipping and dystrophin production as measured by Western blot and dystrophin localization to the sarcolemma as measured by manual PDPF support the robustness of the pharmacologic activity of golodirsen.

Frank 2020 at e2278–79.

52. In December 2019, the FDA granted Vyondys 53® accelerated approval, recognizing "the urgent need for new medical treatments for serious neurological disorders" including DMD—"a rare and devastating disease." Dec. 12, 2019 FDA Press Release.[10] *See also* Vyondys 53® Prescribing Information (Dec. 12, 2019), at § 1. The FDA explained "the data submitted by [Sarepta] demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 53 skipping." Dec. 12, 2019 FDA Press Release at NS00048947. The Vyondys 53® Prescribing Information explains that continued approval may be contingent upon verification of a clinical benefit in confirmatory trials. Vyondys 53® Prescribing Information (Feb. 11, 2021), at § 1.

53. The authors of Frank 2020 noted that "[t]he validated methodology we developed in concordance with current regulatory guidance is the same that was used in previous studies of eteplirsen, therefore allowing a more direct comparison between our current results and the previously published eteplirsen studies." Frank 2020 at e2279. *See also* Schnell 2017[11] (development of a validated Western blot method for quantification of human dystrophin protein used in Phase II and III trials of eteplirsen). The authors of Frank 2020 further reported that "[t]he

[10] Press Release, U.S. FOOD & DRUG ADMINISTRATION, FDA grants accelerated approval to first targeted treatment for rare Duchenne muscular dystrophy mutation (Dec. 12, 2019).
[11] Frederick J. Schnell et al., *Development of a validated Western blot method for quantification of human dystrophin protein used in Phase II and III clinical trials of eteplirsen for the treatment of Duchenne muscular dystrophy (DMD)*, 88 (16 Supplement) NEUROLOGY P5.105 (2017) ("Schnell 2017").

[redacted]

levels of dystrophin detected using Western blot [for golodirsen] exceed the levels previously obtained using eteplirsen, where at week 180, levels of dystrophin in blot ranged from 0 to 2.47 (mean, 0.93; median [calculated], 0.96)." Frank 2020 at e2279. According to Frank 2020, eteplirsen has been "associated with delayed loss of ambulation and halving of the annual decline in respiratory function." *Id.* *See also* § VI.B, *infra*.

54. The results from Part 2 of the golodirsen 4053-101 study are reported in Servais 2022. The primary endpoints were dystrophin protein expression and 6-minute walk test (6MWT). Servais 2022 at 29. The secondary endpoints were percent predicted forced vital capacity (FVC%p) and safety. *Id*. Post-hoc ambulation analyses were performed using mutation-matched external natural history controls. *Id.*; *id.* at 31–32. In particular, the external control patient cohort was matched to the golodirsen-treated group based on mutation class, age, current steroid use, 6MWT distance, and ability to rise from floor. *Id.* at 31–32, 36.

55. Adverse events were generally mild, nonserious, and unrelated to golodirsen, with no safety-related discontinuations or deaths. *Id.* at 29.

56. The below graphs from Servais 2022 demonstrate the golodirsen-induced increase in dystrophin and exon skipping relative to baseline.

[redacted]

Date: *09/06/2023*

Stanley Nelson, M.D.

[redacted]

CERTIFICATE OF SERVICE

I hereby certify that on September 8, 2023, copies of the foregoing were caused to be served upon the following in the manner indicated:

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Exhibit 3 to NS's Response to Sarepta's MIL No. 2

UNITED STATES DISTRICT COURT

DISTRICT OF DELAWARE

Case No. 1:21-cv-01015-GBW

NIPPON SHINYAKU CO., LTD.,

Plaintiff,

v.

SAREPTA THERAPEUTICS, INC.,

Defendant.

SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA,

Defendant and Counter-Plaintiffs,

v.

NIPPON SHINYAKU CO., LTD., and NS PHARMA, INC.,

Plaintiff and Counter-Defendants.

EXPERT REPORT AND DISCLOSURE OF MARK J. HOSFIELD

Submitted September 8, 2023

[redacted]

Before discussing each of the *Panduit* factors, it is relevant to first provide context around the relationship between the named plaintiff in this matter, NS Japan, and its wholly owned subsidiary, NS Pharma, which is the entity that sells VILTEPSO in the U.S. and that competes directly with Sarepta for such sales. I have discussed above in detail the [redacted] Agreement and related MOUs. As described, [redacted].[353] Additionally, NS Pharma's [redacted].[354] Therefore, by virtue of the [redacted] Agreement between [redacted].[355] The *Panduit* analysis below analyzes the lost sales and lost profits of both NS Japan and NS Pharma; however, I note that my quantification of lost profits damages is based on the lost profits realized by NS Japan only.

As discussed above, I understand that NS Japan and NS Pharma do not sell a product covered by the NS patents-in-suit.[356] However, I understand that a patentee is still entitled to recover lost profits as a measure of damages if it markets a product that competes with the infringing product marketed by the infringer.[357] Accordingly, "the first Panduit factor simply asks whether demand existed for the 'patented product,' i.e., a product that is 'covered by the patent in suit' or that 'directly competes with the infringing device.'"[358]

Although the determination as to whether the above factors have been met is a matter for the Court and/or jury to decide, I have detailed my observations regarding each factor below.

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[353] Toda Exhibit 8: [redacted]., dated March 27, 2020 (NS00036906-NS00036908 at NS00036906); Toda Exhibit 9: [redacted] dated April 1, 2021 (NS00036966-NS00036967 at NS00036966); Toda Exhibit 12: [redacted] dated April 1, 2023 (NS00091314-NS00091315 at NS00091314).

[354] Toda Exhibit 8: [redacted] Agreement between Nippon Shinyaku Co., Ltd. and NS Pharma, Inc., dated March 27, 2020 (NS00036893-NS00036908 at NS00036897-NS00036898).

[355] *Callaway Golf Co. v. Acushnet Co.*, 691 F.Supp.2d 566, 575 (D. Del. Mar. 3, 2010); *Intuitive Surgical, Inc. v. Auris Health, Inc.*, 2021 WL 3662842 at *2-3 (D. Del. Aug. 18, 2021); *Polaris Indus., Inc. v. Arctic Cat Inc.*, 2019 WL 1118518 at *7-8 (D. Minn. Mar. 11, 2019); *Schwendimann v. Arkwright Adv. Coating, Inc.*, 220 F.Supp.3d 953, 973-75 (D. Minn. Dec. 12, 2016).

[356] https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=212154&Appl_type=N.

[357] *Rite-Hite Corp. v. Kelley Co.*, 56 F.3d 1538, 1548-49 (Fed.Cir.1995) (en banc); DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F. 3d 1314 (Fed. Cir. 2009); *King Instruments Corp. v. Perego*, 65 F. 3d 941 (Fed. Cir. 1995).

[358] *Rite-Hite Corp. v. Kelley Co.,* 56 F.3d 1538, 1548-49 (Fed.Cir.1995) (en banc); *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F. 3d 1314 (Fed. Cir. 2009).

i. *Panduit* Factor #1: Demand for the Patented Product

In order to prove lost profits, the patentee must show that there was demand for the patented products. I understand such demand can be demonstrated by showing significant sales or use of the products covered by the patents-in-suit and/or competing products.[359]

Demand for VYONDYS 53 is evident based on its unit sales and resulting net sales. Since its commercial introduction in December 2019 through March 2023, Sarepta has distributed more than [redacted] vials of VYONDYS 53 across three broad categories: U.S. paid sales, U.S. free sales, and foreign sales, as summarized in the chart below:[360]

	Sarepta Total Units
Total Units	[redacted]
U.S. Paid Units	
% of Total	
% of Total U.S.	
U.S. Free Units	
% of Total	
% of Total U.S.	
Foreign Units	
% of Total	
% of Total U.S.	

[359] See, for example, *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1330-31 (Fed. Cir. 2009) stating that "the first *Panduit* factor simply asks whether demand existed for the 'patented product,' i.e., a product that is 'covered by the patent in suit' or that 'directly competes with the infringing device.'" (citing to *Rite-Hite Corp. v. Kelley Co.*, 56 F.3d 1538, 1548-49 (Fed. Cir. 1995) (en banc)). See also, *Presidio Components, Inc. v. Am. Tech. Ceramics Corp.*, 702 F.3d 1351, 1360 (Fed. Cir. 2012) stating that "the demand in question in the first *Panduit* factor is not limited to demand for the patented products. Rather, demand may also arise from a product that 'directly competes with the infringing device.'" (citing to the *DePuy Spine* holding).

[360] VYONDYS 53 Financial Summary (SRPT-VYDS-0227829.xlsx, 'Vyondys Summary' tab). Figures for the period of August 1, 2020 through August 18, 2020 were calculated using a proration factor of (18/31) days, and figures for the period of August 19, 2020 through August 31, 2020 were calculated using a proration factor of (13/31) days.

As shown above, sales have increased since VYONDYS 53's launch at the end of December 2019, with an increase of more than [redacted]% from 2020 to 2021, and an approximately [redacted]% increase from 2021 to 2022.[361] All VYONDYS 53 paid sales are sold at a WAC of $[redacted].[362] From the WAC price, additional discounts may be applied,[363] including:

- 340B discounts relate to hospitals that have "preferential pricing, depending on certain criteria."[364] Eligible hospitals "care for a significant share of the nation's underserved populations including children, cancer, and rural patients."[365]
- Medicaid and Tricare discounts are government-mandated discounts for Medicaid recipients and military personnel.[366]
- Data/DIS are discounts to Sarepta's distributors.[367]
- Sarepta's co-pay assistance program which "help[s] offset the co-pays for . . . commercially insured patients."[368]
- Prompt pay is a discount provided to Sarepta's distributors if they pay within a certain period of time.[369]

Through March 2023, Sarepta's total VYONDYS 53 net revenues (which factor in the discounts above) total almost [redacted] and are summarized in the chart below:[370]

Net Sales	[redacted]

[361] Calculated as [redacted].

[362] Deposition of Ryan Wong, dated July 13, 2023, p. 131.

[363] Deposition of Ryan Wong, dated July 13, 2023, pp. 167 and 173.

[364] Deposition of Ryan Wong, dated July 13, 2023, pp. 167-168.

[365] https://www.aha.org/fact-sheets/fact-sheet-340b-drug-pricing-program.

[366] Deposition of Ryan Wong, dated July 13, 2023, p. 168.

[367] Deposition of Ryan Wong, dated July 13, 2023, p. 170.

[368] Deposition of Ryan Wong, dated July 13, 2023, p. 172.

[369] Deposition of Ryan Wong, dated July 13, 2023, p. 173.

[370] Appendix B, Schedules 1A and 1B.

Once NS Pharma's lost profits have been determined, the next step is [redacted] agreement. As described above, [redacted].[491] Thus, in order to determine the amount of NS Pharma's [redacted] Because NS Pharma's lost profits are incremental by nature, these would have directly increased NS Pharma's operating profits. The chart below details the cumulative operating margin NS Pharma actually achieved compared to the cumulative operating margin it would have achieved but-for Sarepta's alleged actions.[492]

Actual Cumulative Operating Profit Margin	[redacted]
But-For Cumulative Operating Profit Margin	

As detailed in the chart above, NS Pharma would have a [redacted] Thus, the difference between the [redacted] sales of VILTEPSO.[493] In total, combined NS Japan lost profits equal approximately $[redacted].[494]

Alternative Lost Profits Calculation

I have performed an alternative lost profits calculation that only calculates lost profits on units sold in the U.S. by Sarepta and excludes any free units. This calculation uses the same methodology as described above and results in total combined lost profits of approximately $[redacted].[495] The details of this calculation are shown throughout the attached Exhibit 3B.

[491] Toda Exhibit 8: License and Supply Agreement between Nippon Shinyaku Co., Ltd. and NS Pharma, Inc., dated March 27, 2020 (NS00036893-NS00036908 at NS00036897-NS00036898).

[492] Exhibit 3A, Schedule 3.

[493] Exhibit 3A, Schedule 3.

[494] Exhibit 3A, Schedule 1.

[495] Exhibit 3B, Schedule 1.

VIII. Prejudgment Interest

I understand that the decision regarding prejudgment interest is a matter for the Court to address. I will perform a calculation of prejudgment interest in such a manner and at such time as the Court may request.

IX. Total Damages

Based on my understanding of the facts and circumstances in this matter, and assuming liability, I have calculated damages measured as a combination of lost profits and reasonable royalties. For the period December 12, 2019 through March 2023 (the last date for which sales data has been provided by Sarepta) total damages equal $[redacted] summarized in the chart below.[591]

Lost Profits and Reasonable Royalty Damages	[redacted]
Lost Profits	
U.S. Paid Units	
U.S. Free Units	
Total Lost Profits Units	
NS Japan Profit per Unit	
NS Japan Lost Profits	
NS Japan Lost Profits from NS Pha	
Total NS Japan Lost Profit Damag	
Reasonable Royalty	
U.S. Paid Units	
U.S. Free Units	
Foreign Units	
Total Reasonable Royalty Units	
Royalty Rate	
Total Reasonable Royalty Damage	
Total Damages	

[591] Exhibit 3A, Schedules 1, 2, 3, and 4. Sarepta has produced data through March 2023. I will be prepared to update my calculations to the extent more recent data is produced.

Reasonable Royalty Damages	
Reasonable Royalty	[redacted]
U.S.Paid Units	
U.S. Free Units	
Foreign Units	
Total Reasonable Royalty Units	
Royalty Rate	
Total Reasonable Royalty Damage	

In addition, I have also calculated the legal fees incurred by NS Japan that I understand are related to Sarepta's alleged breach of the MCA, consisting of "IP Litigation" fees of [redacted] and total "PTAB" fees of [redacted][594]

****

My report, with supporting exhibits, is contained herein, and presents a summary of my opinions and the bases and reasons therefor as of this date. To the extent any additional information is produced by the parties or their experts, I will be prepared to incorporate any such additional information into my report, or otherwise to amend or supplement my report as appropriate.

This report is to be used only for the purpose of this litigation and may not be published or used for any other purpose without prior written consent.

By:

Mark J. Hosfield
September 8, 2023

[594] Exhibit 7, Schedules 1 and 2.

Exhibit 4 to NS's Response to Sarepta's MIL No. 2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	**C.A. No. 21-1015-GBW** [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

REBUTTAL EXPERT REPORT OF JOHN C. JAROSZ

October 11, 2023

[redacted]

117. Mr. Hosfield calculated lost profits of [redacted] based on his assumption that [redacted].[224] Adjusting Mr. Hosfield's lost profits to account for the removal of free units reduces his Scenario 1 claimed lost units from [redacted] and claimed lost profits by [redacted], which is the amount reflected in his Scenario 2.[225]

b. Immediate Ramp Up

118. Mr. Hosfield's calculations relied on the assumption that in the but-for infringement world, NS Pharma would have generated additional VILTEPSO® units in the same month and at the same level that Sarepta sold VYONDYS 53® units in the real-world. That immediate ramp-up conflicts with the real-world business dynamics here.

119. As can be seen in both the entrance of VYONDYS 53® and VILTEPSO® in the real world (and as is typical in new drug launches),[226] there is a natural period of time needed to ramp up sales of a pharmaceutical product, such as VILTEPSO®. For example, NS Pharma only sold 1,166 vials of VILTEPSO® in the first five months of sales (August 19, 2020, through December

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224 Hosfield Report, at p. 108.

225 Rebuttal Tab 6; Hosfield Report, at pp. 108-109.

226 Research shows that pharmaceutical companies need to invest significant time and effort into launch and do not immediately achieve peak sales. Specifically, drug launches may follow an S-shaped curve, with a median time to peak sales of approximately six years, indicating that the early years have a much slower sales trend. *See* Robey, Seth and Frank S. David, "Drug Launch Curves in the Modern Era," *Nature Reviews Drug Discovery* (2017): 1-2. *See also* Charles River Associates, "Is today's pharmaceutical commercial model going extinct?" May 2019, pp. 2-3, available at https://media.crai.com/sites/default/files/publications/LS-One-Time-Therapies.pdf#:~:text=For%20most%20chronic%20therapies%2C%20peak%20sales%20typically%20occur,competitors%20enter%20and%2For%20the%20product%20loses%20patent%20protection. For treatments aimed at rare diseases, like DMD, drug launches are even more difficult and require additional effort (*See* Ascher, Jan et al., "How to successfully launch a rare disease drug in a patient-centric world," January 9, 2017, available at https://www.mckinsey.com/industries/life-sciences/our-insights/how-to-successfully-launch-a-rare-disease-drug-in-a-patient-centric-world#/). Additionally, new products often face a lag while payers are making coverage determinations. In 2019, only a third of patients who attempted to initiate treatment on a new product were able to fill therapy, while more than half faced a formulary restriction and some abandoned due to cost (*See* https://www.iqvia.com/locations/united-states/blogs/2022/01/overcoming-launch-access-barriers-with-patient-support-programs (viewed September 25, 2023)).

[redacted]

2020).[227] VILTEPSO® has seen consistent growth in sales since launch.[228] In fact, Mr. Hosfield acknowledged that NS Pharma "consistently gained patients for VILTEPSO since its launch."[229]

120. Nonetheless, Mr. Hosfield somehow assumed that NS Pharma would have sold [redacted] vials of VILTEPSO® in the first five months of launch (August 19, 2020 through December 2020).[230] In other words, Mr. Hosfield assumed that NS Pharma would have sold over [redacted] vials of VILTEPSO® as it actually did over the same time period, and that there would have been virtually no ramp-up period.[231] For 2021, Mr. Hosfield's analysis assumed that NS Pharma would have sold [redacted] vials of VILTEPSO® on top of the [redacted] vials it actually sold, or approximately [redacted] more vials.[232] Figure 1, below, illustrates the aggressiveness of Mr. Hosfield's analysis as it compares the actual sales of VILTEPSO® over the first 12 months of launch compared with the sales Mr. Hosfield projected as part of his analysis.

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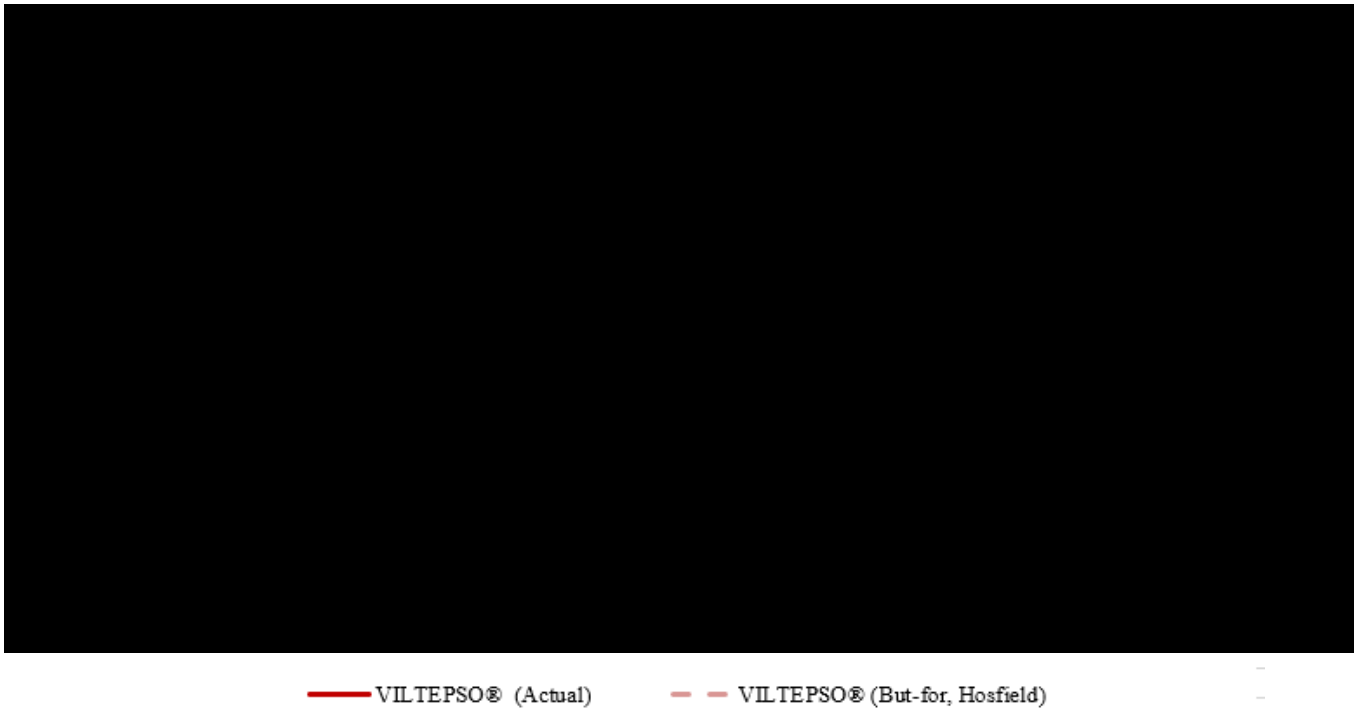
227 Rebuttal Tab 18; Rebuttal Tab 37.
228 *See* Rebuttal Tab 18; Rebuttal Tab 37.
229 Hosfield Report, at p. 77.
230 *See* Hosfield Report, at p. 108. Includes "U.S. Paid Units" of [redacted] and "U.S. Free Units" of [redacted]
231 *See* Hosfield Report, at p. 78; Rebuttal Tab 37. Calculated as [redacted]
232 *See* Hosfield Report, at p. 78; Rebuttal Tab 37. Calculated as [redacted]

[redacted]

Figure 1: Comparison of VILTEPSO® Actual and Hosfield But-For Vial Sales[233]



121. Even assuming NS Japan and NS Pharma had the ability to increase manufacturing and marketing efforts to meet the demand for exon 53 skipping therapies in the absence of VYONDYS 53® at such an accelerated pace, it is unrealistic to assume such sales of VILTEPSO® would have been made by NS Pharma when the corresponding sales of VYONDYS 53® were made by Sarepta. Sarepta was critical in building the business in the real-world, and it took time for it to build momentum. Sarepta would no longer be participating with VYONDYS 53® in the but-for infringement world. NS Pharma would have to build the momentum on its own, which

[233] VILTEPSO® (Actual) values represent actual vials sold in the first twelve months of VILTEPSO® sales (August 2020 through July 2021). *See* Rebuttal Tab 18. VILTEPSO® (But-for, Hosfield) values represent VILTEPSO® vials in the first twelve months of launch, as calculated by Mr. Hosfield. VYONDYS 53® vials used in this calculation include both paid and free units, and values for the first month (August 2020) have been prorated by 13/31 to reflect a launch date for VILTEPSO® of August 19, 2020.

[redacted]

suggests that NS Pharma may have sold *fewer* units in its first few months than it did in the real world.

122. As acknowledged by Mr. Hosfield, "[t]here is evidence that Sarepta has expended more efforts than NS Pharma in terms of marketing and supporting patient advocacy programs."[234] Evidence suggests that NS has identified itself as a "Fast Follower" in the "Exon-Skipping Space" and identified Sarepta as the "1st Mover."[235] As explained by NS, "the Fast Follower gets to take advantage of the market opportunity created by the First Mover."[236] Some of the strategies NS delineated in this regard included "[p]iggy back on existing payer policy."[237]

123. If VYONDYS 53® had not been available, NS Pharma would have had to create its own "market opportunity," and there would be no payer policy to piggyback on, which is suggestive of NS Pharma taking more time to ramp up its sales. As acknowledged by Mr. Hosfield, "Mr. Gendron [redacted]."[238] According to Mr. Gendron, NS Pharma is "[redacted]" and it does not "[redacted]."[239]

124. Evidence suggests there is significant physician and patient loyalty to the Sarepta brand[240] and a low recognition of NS Pharma given its lack of established presence, products, or history in DMD.[241] It is unreasonable to assume that NS Pharma would outperform Sarepta, [redacted]

234 Hosfield Report, at p .71.
235 NS00058280-321, at 300, 306; NS00057814-855, at 840, 841.
236 NS00058280-321, at 307.
237 NS00058280-321, at 308.
238 Hosfield Rebuttal Report, at p. 72; Gendron Deposition, at 169:14-17.
239 Gendron Deposition, at 168:23-169:13.
240 According to Mr. Sudovar, there is resistance in adoption of VILTEPSO® among physicians and patients due to brand loyalty to Sarepta products. Deposition of Stephen Sudovar, July 18, 2023 ("Sudovar Deposition"), at 21:21-22:5.
241 NS00073341-368, at 354.

[redacted], in the 8-month period (December 2019 to August 2020) in which Sarepta faced no competition from NS Pharma.[242] That is, for the 8-month period after VILTEPSO® launched, it would be more appropriate to assume that NS Pharma would not have sold more vials of VILTEPSO® than Sarepta sold in the 8-month period after VYONDYS 53® launched.

125. Adjusting Mr. Hosfield's lost profits to account for the natural ramp-up process reduces his lost vial sales (taking into account paid vials only) from [redacted] and Scenario 2 claimed lost profits by [redacted] percent, from [redacted].[243]

c. Other Impediments to Capture

126. Mr. Hosfield's assumption that [redacted] VYONDYS 53® vials sold between August 19, 2020, and March 2023 would have been captured as paid units of VILTEPSO® at historical actual prices is unfounded for other reasons.

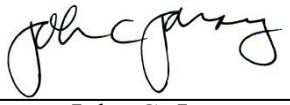
127. Mr. Hosfield did nothing to account for the time between the launch of VYONDYS 53® and the launch of VILTEPSO®, which means that in a but-for world without VYONDYS 53®, patients that were otherwise on an exon 53 skipping therapy would have not had such therapy available to them (though some may have had EXONDYS 51® available to them). This is important because, while Mr. Hosfield assumed all such patients would have started taking VILTEPSO® as soon as it was available, in reality, many such patients may have no longer been able to start such a therapy by the time of VILTEPSO®'s launch. For example, some patients may

[242] VILTEPSO® was approved on August 12, 2020 and VYONDYS 53® was approved on December 12, 2019. *See* https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation (viewed August 3, 2023); https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation (viewed October 11, 2023).

[243] Rebuttal Tab 6; Rebuttal Tab 8.

[redacted]

327. This report is based on the information that was available to me as of the date of this report and summarizes the opinions that I have formed to date. I may revise, supplement, or expand my opinions, if necessary and allowed, based on further review and analysis of information and opinions provided to me before trial.



John C. Jarosz
October 11, 2023

CERTIFICATE OF SERVICE

I hereby certify that on October 11, 2023, copies of the foregoing were caused to be served upon the following in the manner indicated:

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Exhibit 5 to NS's Response to Sarepta's MIL No. 2

UNITED STATES DISTRICT COURT

DISTRICT OF DELAWARE

Case No. 1:21-cv-01015-GBW

NIPPON SHINYAKU CO., LTD.,

Plaintiff,

v.

SAREPTA THERAPEUTICS, INC.,

Defendant.

SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA,

Defendant and Counter-Plaintiffs,

v.

NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC.,

Plaintiff and Counter-Defendants.

REPLY EXPERT REPORT AND DISCLOSURE OF MARK J. HOSFIELD

Submitted October 27, 2023

[redacted]

As an initial matter, I understand from Mr. Gendron that had VYONDYS 53 never entered the market, NS Pharma would have anticipated receiving accelerated approval from the FDA it is reasonable to assume that the FDA would have accelerated the approval of VILTEPSO, leading to an earlier launch. Indeed, Mr. Gendron further explained to me that NS Pharma had anticipated the possibility as early as four weeks after Sarepta received its complete response letter from the FDA denying its new drug application ("NDA") for VYONDYS 53 on August 19, 2019.[15] Such an event would undercut the premise of Mr. Jarosz's ramp-up approach, further proving the speculative nature of the approach.

However, even assuming the FDA did not accelerate the launch date of VILTEPSO, there is still reason to believe that VILTEPSO may not have experienced a ramp-up period similar to that of VYONDYS 53. For example, I understand from my discussion with Mr. Gendron that because it was known that 1) the FDA did not initially approve Sarepta's NDA for VYONDYS 53 because it found that the "very small" clinical benefit of VYONDYS 53 did "not outweigh its risks,"[16] and 2) although direct comparisons cannot be made across studies, dystrophin levels induced by VILTEPSO [redacted],[17] he believes NS Pharma could have sold more units of VILTEPSO and at a faster rate than VYONDYS 53.

Mr. Jarosz also criticizes my assumption that NS Pharma would have been capable of making such additional sales. For example, while he acknowledges my conversations with NS Japan personnel for support of my understanding that NS Japan and NS Pharma would have had the capacity to achieve such sales, he states that "as a matter of economics, it is likely such a dramatic increase in sales would have had some impact on NS Japan or NS Pharma's supply chain. Mr. Hosfield has provided no documentary proof of either company's ability to expand its production to such but-for levels."[18] I have discussed in my Opening Report Mr. Gendron's testimony that NS Pharma's "drug supply is ample"[19] to meet the U.S. demand, as well as my understanding from Mr. Fujii and Dr. Takagaki that NS Japan would have had the flexibility to expand

[15] U.S. Food & Drug Administration Complete Response Letter to Sarepta Therapeutics, Inc., dated August 19, 2019 (NS00096434-NS00096446 at NS00096442).

[16] U.S. Food & Drug Administration Complete Response Letter to Sarepta Therapeutics, Inc., dated August 19, 2019 (NS00096434-NS00096446 at NS00096442).

[17] Safety, Tolerability, and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping, A Phase 2 Randomized Clinical Trial (NS00035339-NS00035348 at

[18] Rebuttal Expert Report of John C. Jarosz, dated October 11, 2023, p. 53.

[19] Rebuttal Expert Report of John C. Jarosz, dated October 11, 2023, p. 53.

	Reasonable Royalty Damages
Reasonable Royalty	[redacted]
U.S. Paid Units	
U.S. Free Units	
Foreign Units	
Total Reasonable Royalty Units	
Royalty Rate	
Total Reasonable Royalty Damage	

****

My Reply Report, with supporting exhibits, is contained herein, and along with my Opening Report and Rebuttal Report, presents a summary of my opinions and the bases and reasons therefor as of this date. To the extent any additional information is produced by the parties or their experts, I will be prepared to incorporate any such additional information into my reports, or otherwise to amend or supplement my reports as appropriate.

This report is to be used only for the purpose of this litigation and may not be published or used for any other purpose without prior written consent.

By:

Mark J. Hosfield
October 27, 2023

[redacted]

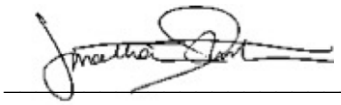
Exhibit 6 to NS's Response to Sarepta's MIL No. 2

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (GBW)
SAREPTA THERAPEUTICS, INC., Defendant and Counter-Plaintiff, and UNIVERSITY OF WESTERN AUSTRALIA, Counter-Plaintiff v. NIPPON SHINYAKU CO., LTD., Plaintiff and Counter-Defendant and NS PHARMA, INC., Counter-Defendant.	

TECHNICAL EXPERT REPORT OF JONATHAN STROBER, M.D.

SEPTEMBER 8, 2023



JONATHAN STROBER, M.D.

decision when choosing therapies to prescribe, how to monitor patients for side effects and benefit and when to prescribe them.

a. Comparisons of Aspects of Exon Skipping Therapies

61. VILTEPSO and VYONDYS 53 are directed at the same patient population (DMD patients with mutations amenable to Exon 53 skipping) and have the same general mechanism of action (binding to exon 53 of dystrophin pre-mRNA to induce skipping of exon 53), although VILTEPSO is a 21-mer and VYONDYS 53 is a 25-mer.[46]

62. Both VILTEPSO and VYONDYS 53 have the same indications and usage. This is confirmed at least by comparing the prescribing information for both products:

VILTEPSO[47]	VYONDYS 53[48]
----------INDICATIONS AND USAGE---------- VILTEPSO is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VILTEPSO. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. (1)	**——————INDICATIONS AND USAGE——————** VYONDYS 53 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with VYONDYS 53. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

63. Further, VILTEPSO and VYONDYS 53 have a similar adverse reaction profile:

VILTEPSO[49]	VYONDYS 53[50]
The most common adverse reactions (incidence ≥15% in patients treated with VILTEPSO) were upper respiratory tract infection, injection site reaction, cough, and pyrexia.	The most common adverse reactions (incidence ≥20% and higher than placebo) were headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea.

[46] Viltepso Prescribing Information 3/2021(https://www.viltepso.com/prescribing-information), Sections 11 (Description) and 12.1 (Mechanism of Action); Vyondys 53 Prescribing Information 2/2021 (https://www.vyondys53.com/sites/vyondys53/files/2022-10/PI.pdf), Sections 11 (Description) and 12.1 (Mechanism of Action).
[47] Viltepso Prescribing Information 3/2021, Indications and Usage.
[48] Vyondys 53 Prescribing Information 2/2021, Indications and Usage.
[49] Viltepso Prescribing Information 3/2021, Adverse Reactions, see also Section 14 Clinical Studies, Adverse Reactions; "pyrexia" means fever.
[50] Vyondys 53 Prescribing Information 2/2021, Section 14 Clinical Studies, Section 14 Clinical Studies, Adverse Reactions.

64. Based on the published data for each of VILTEPSO and VYONDYS 53, at least some patients have experienced a benefit of taking these exon skipping products, as reflected by the primary endpoint measured – increase in dystrophin production. For example, in the clinical trials for each of VILTEPSO and VYONDYS 53, efficacy was measured by change from baseline in dystrophin protein level at a certain time period after treatment (which differs between products):

VILTEPSO[51]	VYONDYS 53[52]
"Efficacy was assessed based on change from baseline in dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 25. Muscle biopsies (left or right biceps brachii) were collected from patients at baseline and following 24 weeks of VILTEPSO treatment, and analyzed for dystrophin protein level by Western blot normalized to myosin heavy chain (primary endpoint) and mass spectrometry (secondary endpoint). In patients who received VILTEPSO 80 mg/kg once weekly, mean dystrophin levels increased from 0.6% (SD 0.8) of normal at baseline to 5.9% (SD 4.5) of normal by Week 25, with a mean change in dystrophin of 5.3% (SD 4.5) of normal levels (p=0.01) as assessed by validated Western blot (normalized to myosin heavy chain); the median change from baseline was 3.8%. All patients demonstrated an increase in dystrophin levels over their baseline values." As assessed by mass spectrometry (normalized to filamin C), mean dystrophin levels increased from 0.6% (SD 0.2) of normal at baseline to 4.2% (SD 3.7) of normal by Week 25, with a mean change in dystrophin of 3.7% (SD 3.8) of normal levels (nominal p=0.03, not adjusted for multiple comparisons); the median change from baseline was 1.9%."	"Efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 48 of Part 2. Muscle biopsies were obtained at baseline prior to treatment and at Week 48 of Part 2 in all VYONDYS 53-treated patients (n=25), and were analyzed for dystrophin protein level by Sarepta western blot. Mean dystrophin levels increased from 0.10% (SD 0.07) of normal at baseline to 1.02% (SD 1.03) of normal by Week 48 of Study 1 Part 2, with a mean change in dystrophin of 0.92% (SD 1.01) of normal levels (p <0.001); the median change from baseline was 0.88%."

[51] Viltepso Prescribing Information 3/2021, Section 14 Clinical Studies.
[52] Vyondys 53 Prescribing Information 2/2021, Section 14 Clinical Studies.

65. In addition to the median changes in dystrophin levels reported, there are individual patient results reported. For VILTEPSO, patients experienced a percent change from baseline of 0.69-13.91.[53] For VYONDYS 53, patients experienced a percent change from baseline of 0.01-3.99.[54]

66. Given the different methods used to quantitate the amount of dystrophin produced from treatment of each drug, it is difficult to compare the benefit of each in order to decide which to prescribe. However, since levels were compared from a baseline, it appears that VILTEPSO has median change of 2-4% dystrophin from baseline, versus VYONDYS 53 which is reported to have a median change of 0.88%, [redacted]. Since dystrophin production was considered a surrogate marker by the FDA for the drugs' approval, in my opinion and evaluation, these differences would favor starting VILTEPSO over VYONDYS 53. I understand there have been no head-to-head studies of these two products, thus physicians must make their own assessment of the currently available information. Based on the sales of VILTEPSO, other physicians have reached a similar conclusion and have elected to prescribe VILTEPSO

67. I evaluated information, including from the sources noted above in making prescribing decisions related to exon skipping therapies for DMD patients, including exon 53 skipping therapies. In selecting between the exon 53 skipping therapies, I elected to recommend VILTEPSO over VYONDYS 53. Specifically, in my practice, I have had the experience of considering what exon 53 therapy would be appropriate to prescribe to an exon 53 amenable DMD patient. On September 28, 2022, this patient presented at the clinic with elevated CPK and developmental delay. Genetic testing was ordered and confirmed DMD with mutation amenable to exon 53 skipping. As part of this patient's treatment, I considered starting corticosteroids and an exon 53 skipper. I discussed possible treatment options with the family, and we agreed to start VILTEPSO at least because of the finding of [redacted] percentage of dystrophin from baseline found in the original studies and the functional data available to date. Other clinicians may have [redacted] come to the conclusion to recommend VILTEPSO or VYONDYS 53 based on their own evaluations.[55] Because the dystrophin data was not obtained in the same way in the VILTEPSO and VYONDYS 53 studies, we do not know how elevated a dystrophin level has to be to make a functional difference.

68. But for VYONDYS 53 being available in the market, VILTEPSO would have been a suitable therapeutic substitute given the indications and usage are the same, the risk profile is similar and both demonstrated an increase in dystrophin production as the primary endpoint.

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[53] Viltepso Prescribing Information 3/2021, Section 14 Clinical Studies, Table 2.
[54] Vyondys 53 Prescribing Information 2/2021, Section 14 Clinical Studies.
[55] I understand that since the launch of Viltepso, according to Sarepta, about [redacted] of patients are now using Viltepso as compared to [redacted] Vyondys 53; Sehinovych Depo. at pp. 167-168. I also understand that Sarepta has observed [redacted]. SRPT-VYDS-0219874.

69. In contrast, AMONDYS is not a suitable substitute for VYONDYS 53 or VILTEPSO. AMONDYS is indicated for treating DMD patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.[56]

70. EXONDYS 51 is indicated for treating DMD patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.[57]

71. DMD patients with only exon 52 mutations are amenable to both exon 51 (EXONDYS 51) or exon 53 skipping (VYONDYS 53 or VILTEPSO).[58] My understanding is that the percentage of patients having only an exon 52 deletion or mutation in this exon is quite small – roughly 3% of all patients with DMD.[59] A smaller portion of those patients are thought to be amenable to exon 53 skipping (0.9% and 1.3%, respectively), given the exon 51 skipping therapy pre-dated the exon 53 exon skipping therapies and would have been available for patients and physicians seeking to prescribe an exon skipper to these patients.[60] This appears to be consistent with Sarepta's understanding.[61]

72. As noted above, EXONDYS 51 was FDA approved over three years prior to VYONDYS 53, and thus the small group of patients with only an exon 52 deletion or mutation would have had the option to seek out exon skipping therapy as early as September 2016 (if not earlier as part of an EXONDYS 51 trial).

73. For exon 52 patients that may have started on EXONDYS 51 prior to VYONDYS 53 being approved, I understand that Sarepta indicated that they maintain information about patients switching between exon-skipping therapies, and Sarepta is not aware of actual reasons a patient may switch from EXONDYS 51 to VYONDYS 53, but theoretical reasons include safety profiles, access, but not dystrophin production (which Sarepta indicates is not comparable).[62] It is possible that a patient that was originally prescribed EXONDYS 51 experienced decline and therefore elected to switch to VYONDYS 53 or VILTEPSO. Given the administrative challenges involved with switching therapies, it is unlikely a patient would switch therapies unless they believe the therapy to which they switch will have a greater clinical benefit.

74. Gene therapy and Other Therapies (PPMO, cell therapies) For the Same Indication

[56] Amondys 45 Prescribing Information (https://www.amondys45.com/pi).
[57] Exondys 51 Prescribing Information (https://www.exondys51.com/sites/default/files/2023-06/EXONDYS51PI.pdf).
[58] Cure Duchenne-Duchenne Population Amenable to Exon Skipping, *see* Exon 51 Skip-amenable "52" and Exon 51 Skip-amenable "52".
[59] Bladen, C.L., et al., The TREAT-NMD DMD Global Database: Analysis of More than 7,000 Duchenne Muscular Dystrophy Mutations. Human Mutation, 2015, Vol. 36, No. 4, 395-402 at 398, Single exon deletions and duplications, Table 2.
[60] Bladen, C.L. (2015) at 399 and Table 2.
[61] Sehinovych Depo. at p. 85; "Only a small subset of the Vyondys 53 population would be amenable to exon 51 skipping. So this would only be if you had a deletion in·52, and I'm not aware that there are any patients with that deletion enrolled in the [Vyondys] trial."
[62] Sehinovych Depo. at pp. 177-185.

75. The FDA has granted accelerated approval to a gene therapy treatment for certain patients with DMD.[63]

76. Specifically, in June 2023, the FDA approved Sarepta's gene therapy product ELEVIDYS for the treatment of pediatric patients 4 through 5 years of age with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene who do not have a pre-existing medical reason preventing treatment with this therapy.[64]

77. ELEVIDYS is characterized as "a recombinant gene therapy designed to deliver into the body a gene that leads to production of Elevidys micro-dystrophin, a shortened protein (138 kDa, compared to the 427 kDa dystrophin protein of normal muscle cells) that contains selected domains of the dystrophin protein present in normal muscle cells."[65]

78. The FDA further noted, "Most current treatment approaches address the symptoms of the disease, but not its underlying genetic cause. Treatments include corticosteroid medications to slow down the progression of muscle weakness, stretching and exercise programs and use of equipment such as braces or a wheelchair as walking becomes more difficult. Antisense oligonucleotides (ASOs) facilitate exon skipping for specific DMD gene mutations, but the ASOs can only address a minority of the gene mutations and require repeated administration."[66]

79. The FDA concluded that "the data submitted by the applicant demonstrated that an increase in this surrogate endpoint (expression of ELEVIDYS micro-dystrophin) is reasonably likely to predict clinical benefit in individuals 4 to 5 years of age with DMD who do not have significant pre-existing antibody titers against the AAV rh74 vector or have other contraindications based on the inclusion criteria of the clinical trials."[67]

80. While the FDA has not imposed any age restrictions on the use of the approved ASO therapies, the FDA has limited the approval of the gene therapy product to the age group (4-5 year olds) in which the clinical trial demonstrated "increased the expression of the ELEVIDYS micro-dystrophin protein."[68] This age range is a narrow segment of DMD patients, for example only 3 of the 65 DMD patients currently in our clinic are 4-5 years old. Patients who are already six years old are not eligible for this therapy.

81. [redacted] For at least this reason and other reasons articulated by the FDA, including those below about adverse events[69], I do not expect there is or will be off-label use of the ELEVIDYS product outside of the indicated age range.

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[63] FDA News Release June 23, 2023, https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treatment-certain-patients-duchenne-muscular-dystrophy.
[64] FDA News Release June 23, 2023; Elevidys Package Insert 2023 (https://www.elevidys.com/PI).
[65] FDA News Release June 23, 2023; Elevidys Package Insert 2023
[66] FDA News Release June 23, 2023
[67] FDA News Release June 23, 2023
[68] FDA News Release June 23, 2023
[69] FDA Center Director Decisional Memo, BLA 125781 (https://www.fda.gov/media/169707/download).

82. Further, the FDA notes that there may be patients not eligible for this gene therapy because they have significant pre-existing antibody titers against the AAV rh74 vector (used to deliver the micro-dystrophin gene) or have other contraindications based on the inclusion criteria of the clinical trials. For example, "Elevidys is contraindicated for patients with any deletion in exon 8 and/or 9 in the DMD gene."[70] ASOs do not include the same exon-based contraindications. There may be other existing conditions in potentially eligible patients that may increase the risk of certain adverse events associated with gene therapy.

83. The FDA is requiring Sarepta to conduct a confirmatory study noting, "[a] clinical benefit of Elevidys, including improved motor function, has not been established. As a condition of approval, the FDA is requiring the company to complete a clinical study to confirm the drug's clinical benefit."

84. The FDA notes that there are potential risks associated with taking ELEVIDYS, including the following adverse events: "The most commonly reported side effects by individuals who received Elevidys were vomiting, nausea, acute liver injury, pyrexia (fever) and thrombocytopenia (abnormally low platelet count in the blood). Patients' liver function should be monitored before treatment with Elevidys, and weekly for the first three months after treatment. Patients given Elevidys may also be at risk for severe immune-mediated myositis (muscle inflammation). Additionally, myocarditis (inflammation of heart muscle) and elevations of troponin-I (a heart protein found in the blood after heart muscle injury) have been observed following use of Elevidys in clinical trials. Troponin-I levels should be monitored before administration of Elevidys and weekly for the first month after treatment."

85. Thus, relatively speaking the adverse events/side effects are much milder and less risky with the exon skipping therapies as compared to ELEVIDYS.

86. Currently, I am not aware of how insurers will view this gene therapy treatment and whether they will agree to pay for it, given the availability of exon skipping therapies.

87. Given the limitations at least on the indications of use, contraindications, adverse event profile, lack of long-term data and unresolved questions regarding insurance coverage, presently, it is unclear whether physicians, families/patients, and insurers will elect to request treatment/cover treatment with this gene therapy product. Based on my experience with other gene therapies, some families may opt out of gene therapy due to the associated risk. The lack of insurance coverage will be a major reason families may opt out of gene therapy. Further, if patients begin on ELEVIDYS, they would not be able to participate in upcoming gene therapy trials with possibly better product. Therefore, younger patients may delay for a year or more to see if they would qualify as studies open.

88. For example, it is unclear whether a patient who is prescribed ELEVIDYS (or another gene therapy product) and later experiences DMD related declines will seek to be prescribed or recommended to take an exon skipping therapy. Or whether FDA approval will be

[70] Deletions of exon 8 and/or 9 appear in number of DMD patient genotypes, including several genotypes of ASO skip-amenable patients (including Exon 8 Skip-Amenable patients). Cure Duchenne-Duchenne Population Amenable to Exon Skipping.

granted for a concurrent gene therapy and exon skipping therapy for DMD patients. For either scenario, it is unclear whether private or public health care insurers will cover the cost of both treatments, giving patients meaningful access to both.

89. I have experienced a similar situation with respect to treatments for Spinal Muscular Atrophy (SMA), another rare genetic condition resulting in muscle weakness due to mutation or deletion of the "survival of motor neuron" gene (SMN1 and SMN2).[71] Recently, in 2019, a gene replacement therapy was FDA approved – ZOLGENSMA (Novartis) for the treatment of SMA.[72] However, prior to the availability of the gene therapy, in 2016, an ASO treatment was available: SPINRAZA (nusinersen, survival motor neuron-2 (SMN2)-directed antisense oligonucleotide)[73].

90. Many families who were eligible for and elected gene therapy had to discontinue the prior treatments and were not approved for the ASO after gene therapy treatment (nor the newer treatment that was approved, EVYRSDI[74] (risdiplam) (Roche)) unless they received free treatment from the company or showed a decline enough to convince insurance companies to cover the cost. A few found clinical trials to participate in to be able to get dual therapy. While the use of ASOs declined after gene therapy, some did not want to take the risk of gene therapy and started or continued ASO therapy and some were placed on it after if gene therapy wasn't as beneficial as we hoped. This change also led to new trials to test the potential safety and efficacy of dual therapy.

[71] Strober, J.B., Tennekoon GI. Topical Review: Progressive Spinal Muscular Atrophies. Journal of Child Neurology. 1999;14(11):691-695. doi:10.1177/088307389901401101.
[72] FDA approved 2019 (https://www.novartis.com/us-en/sites/novartis_us/files/zolgensma.pdf).
[73] FDA approved 2016 (https://www.spinraza.com/content/dam/commercial/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf).
[74] FDA approved 2020 (https://www.gene.com/download/pdf/evrysdi_prescribing.pdf).

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	C.A. No. 21-1015 (JLH) [redacted]
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant/Counter-Plaintiffs, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff/Counter-Defendants.	

SAREPTA THERAPEUTICS, INC. AND THE UNIVERSITY OF WESTERN AUSTRALIA'S REPLY IN SUPPORT OF THEIR MOTION *IN LIMINE* NO. 2 TO EXCLUDE EVIDENCE OR ARGUMENT THAT NS'S COMMERCIAL PRODUCT (VILTEPSO) PERFORMS BETTER THAN SAREPTA'S COMMERCIAL PRODUCT (VYONDYS 53)

[redacted]

Sarepta has no issue with NS arguing that "its product is a suitable alternative to VYONDYS 53." NS Resp. Br. at 1. Sarepta agrees that both parties' products are FDA-approved, safe and effective for the treatment of DMD, and directly compete; indeed, Sarepta is seeking lost profits on that same basis. That is all NS needs for lost profits purposes.

NS represents that it will not argue that "one product is better than the other." *Id*. at 3. But NS betrays its promise by stating that its damages expert will argue that "dystrophin levels induced by VILTEPSO [redacted]." *Id*. at 2 (emphasis added). The fact that one study may report [redacted] than another study under different conditions with different, small patient populations is not a proper point of comparison, and it is not relevant to NS's lost profits case[1] (or any other issue in the case). To allow NS to tell the jury that VILTEPSO [redacted] levels would serve no proper purpose and risks confusing and misleading the jury. Sarepta Op. Br. at 2–3.

NS tries to obfuscate the issue by conflating each product's clinical profile with a ***comparison*** of the products' safety and efficacy.[2] Such a comparison is unreliable, which explains why the FDA will not allow it.[3] While NS can discuss clinical profiles, it should not be permitted to argue or imply that its product is somehow superior to Sarepta's, *e.g.*, by comparing the dystrophin levels reported in two entirely different studies, or putting or discussing them side by side. Any such argument or suggestion would be highly prejudicial and misleading.

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[1] Indeed, comparative dystrophin levels are irrelevant to lost profits, because in that "but for" world, VYONDYS 53 would not be on the market.

[2] For example, NS argues that it is "immaterial" that "the FDA does not allow NS to ***market*** VILTEPSO as superior," because "the FDA approved both VILTEPSO and VYONDYS 53 based on the clinical trial data whose methodology it reviewed." *Id*. at 3 (emphasis in original).

[3] NS counters that Sarepta did not move to exclude the corresponding opinions of NS's experts. *Id.* at 3. But, this motion in limine is the proper avenue to seek preclusion of argument and evidence by NS, including from its attorneys and fact witnesses (in addition to its experts).

[redacted]

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April 29, 2024

CERTIFICATE OF SERVICE

I hereby certify that on April 29, 2024, copies of the foregoing were caused to be served upon the following in the manner indicated:

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